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## Fifteen minutes

### QUINZE MINUTOS

WANDERLEY BERNARDO, JOSÉ MARIA JR., ANTÔNIO SALOMÃO, EDMUND BARACAT

<http://dx.doi.org/10.1590/1806-9282.60.05.001>

#### **DESCRIBING THE IMPORTANCE OF OBESITY TODAY, AND THE LACK OF STRATEGIES FOR PROPER MANAGEMENT, CAN TAKE FIFTEEN MINUTES OF READING, BUT THE PROBLEM MUST INVOLVE MUCH MORE TIME OF YOUR ATTENTION, AS WELL AS GUIDANCE TO YOUR PATIENTS.**

Epidemic and rising rates of obesity in many parts of the world are leading to increased suffering and economic stress. Despite decades of research on the causes of the obesity pandemic, which does not seem close to a solution, there is still no clear understanding of the nature of the problem. This limits creativity and suffocates expansive thinking, which could advance in the field of prevention and treatment, as well as in the scope of the complications of obesity. Shared decision-making and the redirecting of policies could remove barriers that prevent us from moving forward to solve an urgent public health issue of the beginning of this century<sup>1,2</sup>.

Overweight and obesity reflect a gain of excess body fat, including visceral fat, which is a result of initially imperceptible cumulative effects of everyday eating, hourly, with no proper physical activity, creating a surplus of calories consumed in relation to those expended. Excess weight gain, gradual and unintended, is accompanied by the difficulty of reversing the picture and can become permanent. Even if all currently obese patients were treated effectively in the absence of adequate preventive efforts, there would still be continued growth in the number of obese people. Many multifaceted interventions to prevent obesity seek to influence the balance of calories, focusing on energy consumption, or energy expenditure. While obesity is a priority from an epidemiological and public health perspective, it becomes even more important as it influences other aspects of society. Substantial direct and indirect costs include discrimination, economic deprivation, loss of productivity and disability. Thus, state and local governments end up diverting resources for prevention and treatment. The country's health system is burdened with the comorbidities of obesity, such as type 2 diabetes, hypertension, cardiovascular diseases, osteoarthritis and cancer. It is estimated that the annual burden of obesity is almost 10% of all medical spending<sup>3</sup>.

There are programs of shared decision-making that offer surgical treatment modalities for weight loss, including:

Roux-en-Y gastric bypass, laparoscopic adjustable gastric banding and laparoscopic sleeve gastrectomy. Patients attend seminars where they are instructed on the differences in outcomes, follow-up and complications of each procedure. The main information presented at the seminar include: 1. Greater weight loss with Roux-en-Y and sleeve gastrectomy compared to the use of a gastric band; 2. The gastric band requires the highest number of post-operative visits (monthly in the first year); 3. The Roux-en-Y and the sleeve gastrectomy have a higher rate of life-threatening complications than the gastric band (fistula); 4. The gastric band has highest number of delayed complications related to the device (erosion, migration); 5. The Roux-en-Y has the highest rate of diabetes remission; and 6. There is a lack of data on five-year follow-up of weight loss after sleeve gastrectomy. Fifty-eight percent of patients chose "weight loss" as the most important result, and 65% chose "fistula" as the most worrisome complication. A subgroup analysis including patients with diabetes showed that 58% chose "curing diabetes" as the most important result. Nineteen percent of patients were unsure about which procedure they wanted, or changed their decision after consultation with the surgeon<sup>3</sup>.

#### **THE CHOICE FOR BARIATRIC SURGERY IS NOT EASY, AND SHARED DECISION-MAKING IN THE MANAGEMENT OF OBESITY SHOULD ADDRESS BOTH THE MEDICAL AND SURGICAL TREATMENT, AND PREVENTION, REQUIRING MORE THAN FIFTEEN MINUTES.**

In decision-making, patients can choose to be more passive. That is because they do not know how to feel when they are more active in decisions. Or, they may fear abandonment or being labeled "difficult if they seem to defy the doctor's authority. They may find it difficult to tolerate the doubt, being satisfied with the first solution, less than ideal, but available. In turn, physicians may assume that the patient made the decision based on correct information and appropriate assumptions, especially if the professional opinion is naturally favored. It is generally accepted that whenever patients are well-informed, they can make the best decisions. Patients often want more information than expected. Sometimes, however, the more information is presented, the worse is the understanding of patients. Patients and physicians need to consider the right amount. In addition, the number and types of suitable options (not all possible options at once) and

the right time to accommodate the limits of individual and shared cognitive processing. Physicians should be alert to the potential of hierarchical relationships that can promote coercion or silence the voice of the patient, and regularly check for understanding. They should also be aware of the indirect signs of emotional distress and demonstrate reliability and transparency, actively soliciting the patient's questions and concerns. Self-knowledge, self-monitoring, honesty and the willingness to challenge one's own assumptions are key qualities, which, when cultivated by the physician, will help him/her distinguish his/her participation in increasing autonomy at the expense of well-meaning, but mistaken, imposition of values<sup>4</sup>.

### **PROPER PATIENT CARE REQUIRES DIALOGUE WITH REGARD TO OPTIONS AND DECISIONS, WHICH IS NOT ACCOMPLISHED IN 15 MINUTES.**

• **Talking about choices.** How to get patients to understand that there are reasonable options? The components of this stage are: a) Step one – Summarize and say: “Now that we have identified the problem, it's time to think about what to do next”; b) Offer choices - Please note that patients often misinterpret the presentation of choices and think the doctor is either incompetent or uninformed, or both. Reduce this risk by saying: “There is good information about how these treatment options differ, and I would like to discuss this with you”; c) Justify the choice - Emphasize: 1) The importance of respecting individual preferences; 2) The role of uncertainty. *Customize preferences:* explain that different issues are more important to some people than to others, which should be easily understood. Say: “Treatments have different consequences. Some will be more important to you than to others.” *Uncertainty:* Patients often are unaware of the extent of uncertainty in medicine, how evidence can be weak and the results, unpredictable at the individual level. Say: “Treatments are not always effective, and the chances of suffering side effects vary.” d) Check the patient's reaction – The choice among options can be confusing: some patients may express concern. Suggested phrases: “Let's continue” or “Should I tell you about the options?” e) Postpone the end of the conversation – Some patients react asking doctors: “Tell me what to do.” Postpone the end in case this occurs, assuring your patient that you are willing to support his/her decision-making process. Say: “I'm happy to share my opinions and help you reach a good decision. But before I do that, can I describe the options in more detail so that you understand what is at stake?”<sup>5</sup>

• **Talking about the options:** a) Check their knowledge - Even well-informed patients may be only partially awa-

re of the options, and the harms and benefits associated with the procedures, or they may be misinformed. Evaluate with the question: “What have you heard or read about the treatment of obesity?”; b) Write the options - Make a clear list of alternatives, as this offers good structure. Say: “Let me list the options before we go into more detail”. If this is the case, add the option “wait watching” or use positive terms such as “active monitoring”; c) Describe the options (in practical terms) - Generate dialogue and explore preferences. If there are two medical treatments, says: “Both options are similar and involve taking medication regularly.” Point out when there are clear differences (surgery or medication), situations in which it is possible to postpone, or those in which decisions are reversible. Say: “These options have different implications for you in relation to others, and so I want to describe ...”. Harm and benefits - Being clear about the pros and cons of the different options is crucial in shared decision-making. Learn effective communication about risk, effects of the process, importance of providing data on absolute risk, as well as in relative terms; d) Support the patient's decision – Synthetic tools make the options visible and can save time. Some are sufficiently concise to use in clinical visits. Examples: cards related to the subject, decision charts and option tables. Shared decision may need more than a medical visit. More extensive tools for patient decision support can play a crucial role. Say: “These tools are designed to help you understand the options in more detail. Use them and come back so that I can answer your questions.” e) Summarize - List the options again and assess understanding, asking reformulations<sup>5</sup>.

• **Talking about the decision:** a) Focus on preferences - Guide the patient to express them. Suggested phrases: “What, from your point of view, is more important to you?” b) Inducing a preference - Be prepared to provide additional time or willing to guide the patient if he/she indicates that this is his/her wish; c) Move to a decision - Try to verify the need to postpone the decision or take it. Suggested phrases: “Are you ready to decide?” / “Do you want more time?” / “Do you have any other questions?” / “Is there anything else that we need to discuss?” d) Review the offer – Reminding the patient, whenever possible, that decisions can be reviewed is a good way to end the conversation<sup>5</sup>.

Briefly, patients must decide not only through a theoretical exercise, but considering the context that preserves the expression of their autonomy, in which there must be: clarity on where the care is provided; about the treatment process or outcome to achieve a particular health

status; adequate information regarding their preferences; perceived credibility of the information source; clarity in the language used to describe options; attention to different attributes of a decision such as benefits and harms; number of options available; valuing of previous experiences in similar situations; affection; description of the effects in the order in which they occur; analysis of reliable opinions of others; perceived social norms; and media influence<sup>6</sup>.

Modalities that lead to rapid, invasive and irreversible solutions used in the treatment of obesity, which grow exceeding their applications, occupy the space of absence or failure of preventive measures and medical treatment.

Reading this walkthrough of shared decision-making can be done in just fifteen minutes. However, in order to care for patients who suffer, and health systems that do not know how to preserve them, medicine is in urgent

need of much more than fifteen minutes of dedication. The consequences of a poor decision can last more than fifteen minutes, hours, days, months, years or decades.

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## Update on angle-closure glaucoma: treatment

### ATUALIZAÇÃO EM GLAUCOMA DE ÂNGULO FECHADO: TRATAMENTO

BERNARDO WM, PRATA TS, KANADANI FN, SIMÕES R

<http://dx.doi.org/10.1590/1806-9282.60.05.002>

**1. On prophylactic laser iridotomy, in the contralateral eye, in a patient with acute primary angle closure in one eye, we can affirm that:**

- It can prevent similar episodes in many cases.
- There is no increase in intraocular pressure (IOP) in treated cases.
- Cases with higher IOP have less chances of requiring additional treatment.
- In such cases, surgical iridectomy should be preferred over laser iridotomy.

**2. The differences between prophylactic laser iridotomy (PLI) and prophylactic surgical iridectomy include:**

- PLI is more effective.
- PLI costs less.
- The surgical procedure is safer.
- The surgical procedure is more effective.

**3. It is not a complication of PLI:**

- Acute IOP rise.
- Anterior uveitis.
- Clinical improvement of cataract.
- Corneal decompensation.

**4. Which anatomic situation of the camerular sinus is an indication for prophylactic laser iridotomy?**

- All cases of suspected primary angle closure.
- All cases diagnosed as primary angle closure.
- In cases without adhesions but with the presence of imprint.
- All cases of occludable angle, but with normal IOP and absence of adhesions and/or imprint.

**5. Factors involved in the indication of PLI in cases of suspected primary angle closures include all of the following, except:**

- Lack of symptoms.
- Family history of glaucoma or blindness.
- Patient follow-up capacity.
- Social and economic status.

### ANSWERS TO CLINICAL SCENARIO: ANGLE-CLOSURE GLAUCOMA: DIAGNOSIS [PUBLISHED IN RAMB 2014; 60(4)]

**1. What is the importance of gonioscopy in the diagnosis of patients with angle-closure glaucoma?**

This is the most relevant examination for the classification of glaucoma. (Alternative B)

**2. What is the role of UBM (Ultrasound Biomicroscopy) in the diagnosis of patients with angle-closure glaucoma?**

The apposition of the iris to the outer wall of the camerular sinus has been more frequently detected by UBM than gonioscopy. (Alternative C)

**3. What is the role of AS-OCT (Anterior Segment Optical Coherence Tomography) in the diagnosis of patients with angle-closure glaucoma?**

AS-OCT is useful for quantitative evaluation of the camerular sinus. (Alternative D)

**4. Can AS-OCT replace gonioscopy?**

There is greater concordance between the two methods in detecting closed angles in the upper quadrants. (Alternative B)

**5. What is the validity of the prone-position test in dark room in the diagnosis of angle-closure glaucoma?**

Checking the probability of angle closure when there is IOP elevation. (Alternative C)

## Update on late-onset hypogonadism (LOH) or ADAM: diagnosis

### ATUALIZAÇÃO EM HIPOGONADISMO MASCULINO TARDIO (HMT) OU DAEM: DIAGNÓSTICO

BERNARDO WM, MARTITS AM, COSTA EMF, NARDI AC, NARDOZZA JR. A, FARIA G, FACIO JR. FN

<http://dx.doi.org/10.1590/1806-9282.60.05.003>

- 1. The main signs and symptoms involved in late-onset male hypogonadism include the following, except:**
  - a. Erectile dysfunction and decreased libido.
  - b. Anxiety.
  - c. Depression.
  - d. Decreased testicular volume.
  
- 2. On the main instruments used in the definition and diagnostic assessment of male aging, we cannot affirm that:**
  - a. When analyzing the responses to the ADAM questionnaire, clinically suspected cases of LOH are those in which the symptoms of sexual dysfunction are present.
  - b. The Smith questionnaire is considered a questionnaire to assess the risk of LOH.
  - c. It is recommendable for the AMS scale and ADAM questionnaire to be used as screening instruments.
  - d. The use of the three instruments makes the diagnosis of HMT through functional and biochemical criteria unnecessary.
  
- 3. What is the role of the serum and free testosterone (BAT) levels in the diagnosis of late-onset hypogonadism?**
  - a. Free testosterone is a less precise marker of hypogonadism.
  - b. The result of the total testosterone level does not affect the determination of free testosterone.
  - c. TT (total testosterone) would not be the ideal measure to assess late-onset hypogonadism.
  - d. There is a fall in testosterone and BAT levels at 2.3%/year and 1.1%/year.
  
- 4. Tests to be requested before the start of hormone replacement therapy (ART) include the following, except:**
  - a. Baseline testosterone measurement.
  - b. Lipid evaluation.
  - c. Baseline PSA levels.
  - d. Evaluation of renal function.
  
- 5. How should prostate cancer be monitored?**
  - a. Ultrasound-guided prostate biopsy.
  - b. PSA higher than 4 ng/mL or 3 ng/mL in men with a high risk of prostate cancer.
  - c. An increase in PSA levels higher than 1.4 ng/mL in any 12 month period during treatment.
  - d. Detection of prostatic abnormality during rectal examination.

## Degenerative spondylolisthesis: surgical treatment

### ESPONDILOLISTESE DEGENERATIVA: TRATAMENTO CIRÚRGICO

**Authorship:** Brazilian Society of Neurosurgery; Brazilian Society of Orthopedics and Traumatology

**Participants:** Ricardo V. Botelho; Noel O. Foni; Alberto O. Gotfryd; Carlos Fernando P.S. Herrero; Jefferson Daniel; Robert Meves; Marcelo Luis Mudo; Ricardo S. Simões; Sérgio Zylbersztejn; Wanderley M. Bernardo

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*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.*

*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

### DESCRIPTION OF THE EVIDENCE

#### COLLECTION METHOD

To develop this guideline the following primary and secondary electronic databases were consulted: Medline (1966-2009), Cochrane, Cochrane Central Register of Controlled Trials – Central, Embase (1980-2010) and Lilacs (1982-2010). The search for evidence came from actual clinical scenarios and used keywords (MeSH terms) grouped in the following syntax: surgical procedures, operative, nonsurgical, therapy, lumbosacral region, lumbosacral, degenerative, spondylolisthesis, spondylolisthesis. The articles were selected after critical evaluation of the strength of scientific evidence by specialists from the participating Medical Associations, and publications of greatest strength were used for recommendation. The recommendations were drawn from group discussion. The entire guideline was reviewed by an independent group specializing in evidence-based clinical guidelines.

#### GRADE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

- A. Experimental or observational studies of higher consistency.
- B. Experimental or observational studies of lower consistency.
- C. Case reports (non-controlled studies).
- D. Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

#### OBJECTIVE

This guideline's target audience comprises general practitioners, rheumatologists, orthopedists, physiatrists, neurologists and neurosurgeons in order to be able to guide patients with lower back pain and/or sciatic pain resis-

tant to non-operative treatment caused by lumbar degenerative spondylolisthesis regarding the indication for surgical treatment.

#### INTRODUCTION

Degenerative spondylolisthesis refers to a forward slippage of a lumbar, with an intact neural arch. Uncommon before the age of 50 years, it is more common in women and particularly in blacks, with a male: female ratio of 1:6 (B).<sup>1</sup> L4-L5 is the most commonly affected level and rarely exceeds 30% of the vertebral width. Degenerative spondylolisthesis is usually asymptomatic but may be associated with symptomatic stenosis of the lumbar spinal canal. The canal stenosis is the most common cause of back surgery in adults over 65 years when associated with neurogenic claudication. However, spinal stenosis is usually asymptomatic. Therefore, clinical radiological correlation is essential for making decisions (A).<sup>2</sup> Surgical treatment with spinal decompression and stabilization in spondylolisthesis is recommended when conservative treatment fails (B).<sup>3</sup>

#### HOW LONG SHOULD CONSERVATIVE TREATMENT (NON-OPERATIVE) BE MAINTAINED?

In general, favorable functional outcomes in patients unresponsive to non-operative treatment are reported in groups with diverse etiologies for degenerative lumbar stenosis as well as time of conservative treatment (C).<sup>4-6</sup> The time tested in this particular group of patients included in the clinical trial was 12 weeks. Patients treated conservatively without success and who underwent surgical treatment had better progression from a functional point of view, after 4 years of follow-up (B).<sup>7</sup>

### Recommendation

After 12 weeks of unsuccessful conservative treatment, surgery is a treatment option for these patients (B).

### IS IT NECESSARY TO REFER THE PATIENT TO ARTHRODESIS WITH USE OF RIGID PEDICLE SCREWS (NON-DYNAMIC)?

The trials below discussed the value of fusion as treatment for spinal stenosis associated on one or two levels with degenerative spondylolisthesis.

Herkowitz and Kurz<sup>8</sup> studied the isolated non-instrumented arthrodesis and showed that fusion produced less radicular pain (in the lower limbs) and better clinical outcome according to the surgeon's assessment (B).<sup>8</sup> Bridwell et al.<sup>9</sup> compared instrumented and non-instrumented fusion techniques. Patients undergoing instrumented fusion had less progression of spondylolisthesis and improved walking ability (B).<sup>9</sup> Obtaining solid fusion was associated with subjective improvement. Both studies have methodological limitations: the control group was small (B).<sup>8,9</sup>

Fishgrund et al.<sup>10,11</sup> in a randomized trial done in 1997, studied the effect of instrumentation on outcomes of spondylolisthesis, either arthrodesed or not. The authors found that the instrumentation increased the fusion rate but did not improve clinical outcomes (B).<sup>10,11</sup> These studies have provided conflicting evidence according to which instrumentation would produce significant clinical improvement.

### Recommendation

Instrumentation is an option in the treatment of degenerative spondylolisthesis to increase the chance of obtaining solid fusion and improve clinical outcomes (B).

### IS THE USE OF BONE SUBSTITUTES SUCH AS BMP (BONE MORPHOGENETIC PROTEIN) SAFE AND EFFECTIVE IN LUMBOSACRAL ARTHRODESIS?

Regarding the rate of fusion, two studies<sup>12-14</sup> compared the use of osteoinductors (BMP) with iliac graft in patients with degenerative spondylolisthesis (single level), treated by means of neural decompression and non-instrumented intertransverse arthrodesis, with similar clinical and radiographic results (B). However, there are many publications and case reports on complications arising from the use of BMP, including bone resorption and osteolysis, cage/graft migration, heterotopic ossification, radiculitis, formation of specific antibodies and bruises.<sup>15</sup> Prospective and randomized studies are needed to elucidate the best clinical indications and safe dosages for the use of osteoinductors (BMP) in lumbosacral spine.

### Recommendation

Due to the small number of studies on osteoinductors (BMP) and the high number of complications arising from their use, it was not possible to recommend its routine use for the treatment of these patients.

### WHAT IS THE MOST APPROPRIATE DIAGNOSTIC STUDY IN THIS CLINICAL CONTEXT?

Plain radiographs in the standing position determine the diagnosis and the percentage of slippage in degenerative spondylolisthesis. Being available in most hospitals and since it is not an invasive test, this is the first additional test requested (C).<sup>16,17</sup> Plain radiographs of the spine are effective to evaluate the bone structure of the spine and should be performed in the standing position to be more accurate in identifying the intervertebral disc height, lumbar lordosis and the degree of slippage between the *vertebrae*. Plain radiographs in anteroposterior incidence also allow assessment of the morphology of the articular facets. The lateral view also allows dynamic evaluation of the stability of the spine with studies of lumbosacral spine in maximum flexion and extension (C).<sup>22</sup>

Computed tomography is more sensitive and specific in identifying the narrowing of the spinal canal than plain radiography, because it allows visualization of the spinal canal in axial view. Myelography or CT myelography is more specific than non-specific CT scans and is important for the identification of spinal stenosis in patients with degenerative spondylolisthesis and neurologic symptoms. However, this is a test rarely used because it is invasive and is associated with adverse effects – secondary to ionizing radiation and contrast injection (C).<sup>18,19</sup>

In the presence of symptomatic lumbar stenosis, the most sensitive and specific radiologic examination is MRI, as it enables the visualization of soft tissues in the spine. MRI is the most accurate study to analyze the pathological anatomy of the narrowing of the spinal canal – produced by prolapsed intervertebral disc, hypertrophy of the *ligamentum flavum*, zygapophyseal joint hypertrophy, and vertebral slippage with intact vertebral arch (C).<sup>20</sup> Dynamic myelography and CT myelography may be indicated to elucidate cases where there is a lack of association between symptoms and MR imaging for dynamic analysis or the presence of bony component contributing to the narrowing of the spinal canal. Another possibility for such an indication is MRI contraindicated in patients with pacemakers and claustrophobia. Sedation and open MRI are options for performing the test in patients with claustrophobia (C).<sup>17-21</sup>

### Recommendation

The most appropriate diagnostic test in this situation is plain radiography, which is more widely available; however, MRI is indicated for patients with symptomatic lumbar stenosis.

### BONE SUBSTITUTES ARE EQUAL OR SUPERIOR TO AUTOGRAFTS IN THIS SITUATION?

Two randomized trials<sup>23,24</sup> evaluated the association of bone expander beta-tricalcium phosphate to “local” bone tissue from the posterior vertebral elements, and compared their achieved results with autologous iliac graft, considered the gold standard in this clinical scenario. Both studies reported there were no clinical or radiographic differences between the groups assessed, and the use of bone expanders avoided the occurrence of pain in the iliac donor site (A).<sup>23,24</sup>

### Recommendation

The association of local bone graft (from the posterior vertebral elements) and beta-tricalcium phosphate is a therapeutic option for the removal of autologous bone graft from the iliac bone (A).

### SHOULD THE SPONDYLOLISTHESIS BE REDUCED?

In the search for Keywords and indexed terms, 388 articles were retrieved; of these, 47 abstracts, and 3 comparative clinical trials chosen for analysis. A thorough analysis showed that the three articles were case series with small samples, and two showed a 60% loss on follow-up and conflicting results (C).<sup>25-27</sup> Due to the low quality of the articles, it was not possible to make a recommendation.

### ARE THERE ANY DIFFERENCES AMONG THE VARIOUS TYPES OF ARTHRODESIS?

There are no randomized trials comparing the various methods of arthrodesis focusing on degenerative spondylolisthesis, especially with regard to intersomatic spacers. We found that lower-quality observational studies using different techniques for lumbar fusion and heterogeneous study populations showed a higher fusion rate in patients undergoing circumferential arthrodesis, but without evidence of better functional results (B).<sup>28-30</sup>

### Recommendation

There are no randomized trials comparing the various methods of arthrodesis and use of intersomatic spacers in cases of degenerative spondylolisthesis; thus, it is not possible to recommend a specific technique (B).

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## Late-onset hypogonadism or ADAM: treatment

### HIPOGONADISMO MASCULINO TARDIO OU DAEM: TRATAMENTO

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*The Guidelines Project, an initiative of the Brazilian Medical Association, aims to combine information from the medical field in order to standardize procedures to assist the reasoning and decision-making of doctors.*

*The information provided through this project must be assessed and criticized by the physician responsible for the conduct that will be adopted, depending on the conditions and the clinical status of each patient.*

### DESCRIPTION OF THE EVIDENCE COLLECTION METHOD

The recommendations were supported by the evidence obtained in the Medline, Embase, Lilacs and Cochrane databases, using the following strategies: (((((aged OR aging) AND (androgens/deficiency OR hypogonadism OR testosterone/deficiency)) AND (hormone replacement therapy) AND (aging/blood OR androgens/blood\* OR androgens OR androstenedione/blood OR body mass index OR body Weight OR dehydroepiandrosterone/blood\* OR dehydroepiandrosterone sulfate/blood\* OR dihydrotestosterone/blood OR gonadal steroid hormones/blood\* OR gonadotropins/blood OR gonadotropins OR pituitary hormones OR hormones/blood\* OR hormones/physiology OR hypogonadism/blood OR hypothalamo-hypophyseal system OR immunoassay OR luteinizing hormone OR luteinizing hormone/blood OR radioimmunoassay OR radioimmunoassay/methods OR radioimmunoassay/standards\* OR reagent kits, diagnostic/standards OR sex hormone-binding globulin/analysis OR testosterone OR testosterone/blood\* OR testosterone/metabolism OR hematocrit OR liver function tests OR prostatic neoplasms OR continuity of patient care OR consultation OR monitoring))) AND (diagnosis/broad[filter] AND ("last 5 years"[PDat]))) OR (((((aged OR aging) AND (androgens/deficiency OR hypogonadism OR testosterone/deficiency)) AND (hormone replacement therapy) AND (aging/blood OR androgens/blood\* OR androgens OR androstenedione/blood OR body mass index OR body weight OR dehydroepiandrosterone/blood\* OR dehydroepiandrosterone sulfate/blood\* OR dihydrotestosterone/blood OR gonadal steroid hormones/blood\* OR gonadotropins/blood OR gonadotro-

pins OR pituitary hormones OR hormones/blood\* OR hormones/physiology OR hypogonadism/blood OR hypothalamo-hypophyseal system OR immunoassay OR luteinizing hormone OR luteinizing hormone/blood OR radioimmunoassay OR radioimmunoassay/methods OR radioimmunoassay/standards\* OR reagent kits, diagnostic/standards OR sex hormone-binding globulin/analysis OR testosterone OR testosterone/blood\* OR testosterone/metabolism OR hematocrit OR liver function tests OR prostatic neoplasms OR continuity of patient care OR consultation OR monitoring))) AND (etiology/broad[filter]) (age OR aged OR aging) AND (andropause OR gonadal OR deficiency OR hypogonadism OR hypogonadal) AND (testosterone OR androsterone OR DHEA OR dehydroepiandrosterone OR androgen OR androgenic OR nandrolone OR replacement OR steroids OR anabolic OR sex OR hormone) AND (muscles OR strength OR cognitive OR function OR cognition OR mental OR performance OR diabetic OR diabetes OR obesity OR body OR fat OR obese OR mass OR hyperinsulinaemia OR adiposity OR libido OR sexual OR behavior OR quality of life OR life style OR lipids OR carbohydrates OR metabolism) ((age OR aged OR aging) AND (andropause OR gonadal OR deficiency OR hypogonadism OR hypogonadal) AND (testosterone OR androsterone OR DHEA OR dehydroepiandrosterone OR androgen OR androgenic OR nandrolone OR replacement OR steroids OR anabolic OR sex OR hormone))) AND (polycythemia OR prostatic neoplasms OR cardiovascular diseases OR liver diseases OR sleep apnea syndromes OR metabolic syndrome).

## GRADE OF RECOMMENDATION AND STRENGTH OF EVIDENCE

**A:** Experimental and observational studies with high consistency.

**B:** Experimental and observational studies with low consistency.

**C:** Case reports (non-controlled studies).

**D:** Opinions without critical evaluation, based on consensus, physiological studies, or animal models.

## OBJECTIVE

To recommend evidence-based approaches to treat late-onset hypogonadism.

## INTRODUCTION

The benefits of androgen replacement therapy in hypogonadal young men are well documented, especially given that the restoration of testosterone concentrations to normal limits maintains and restores sexual function, energy, mood, the development of muscle mass and increases bone mass. However, the cost/benefit relationship of testosterone replacement in Androgen Deficiency in the Aging Male (ADAM) remains controversial (A).<sup>1</sup>

## WHAT IS THE ROLE OF ANDROGEN REPLACEMENT THERAPY (ART) TO RESTORE BONE MASS, MUSCULAR STRENGTH AND BODY COMPOSITION?

There is no doubt that ART has a positive effect on bone mass. The treatment with testosterone determines a significant improvement in bone mass in hypogonadal men of all ages (B).<sup>2</sup> This effect becomes even more evident the longer the treatment time and the more severe the hypogonadism (A).<sup>3</sup>

The effects of ART on muscular strength in men with ADAM are generally evaluated indirectly through analysis of the performance of physical activities and body composition. Therefore, the use of transdermal testosterone at a dose of 50mg/day for a 6 month period has been shown to be capable of increasing muscular strength and lean mass in patients, improving their physical function and quality of life (A).<sup>4</sup> Direct evaluation of muscle size in elderly patients with chronic diseases with a loss in muscle mass and ADAM have shown that testosterone therapy in older patients leads to an increase in muscle size and improved muscular strength, improving performance in physical activities (B).<sup>5</sup>

The most reproducible effect of testosterone treatment is the increase in lean mass both in hypogonadal patients and healthy males. Even if for a short period of

time, transdermal testosterone treatment increases muscle mass in hypogonadal men aged over 40 years (A)<sup>3</sup>(B).<sup>6</sup>

On the other hand, studies evaluating the reduction in body fat as a direct effect of testosterone treatment are controversial. A slight reduction in body fat in patients being treated has sometimes been observed (A).<sup>3</sup> Testosterone treatment results in a significant reduction in waist circumference, which is an indicator of visceral fat (A).<sup>7</sup> However, this benefit has not been shown in short acting treatments (A).<sup>8</sup>

The reduction in BMI and waist circumference may not occur in all patients, but the reduction in visceral fat is evident when analyzed directly using magnetic resonance imaging. Therefore, testosterone therapy selectively reduces the accumulation of visceral fat, though the change in total body composition is not observed in all patients (B)<sup>6</sup>(A).<sup>9</sup>

This discrepancy in the findings in relation to the effects of testosterone on the reduction of lean mass may be related to the dose or route of testosterone administration, or the direct effect of testosterone on the increase in lean mass. Ultimately, testosterone replacement improves the body composition of patients with low levels of the hormone (B).<sup>2</sup>

The use of GH in association with testosterone appears to present a synergic effect on the improvement in body composition, muscular strength and, consequently, the quality of life of men with ADAM, and can be a treatment option to be considered in such patients (A).<sup>10,11</sup>

## Recommendation

Testosterone replacement therapy improves bone mass, muscular strength and body composition in patients with ADAM and the effects increase with the length of treatment and severity of hypogonadism. The use of testosterone in patients with ADAM is strongly recommended to increase bone mass, muscular strength and body composition.

## WHAT IS THE ROLE OF ANDROGEN REPLACEMENT THERAPY (ART) TO RESTORE LIBIDO AND SEXUAL FUNCTION?

The effectiveness of testosterone replacement therapy on sexual symptoms has been well established, regardless of the route of administration; nevertheless, the works are controversial in relation to the effectiveness of the oral route. Treatment with testosterone, regardless of the route of administration, improves and restores the libido in men with lower testosterone levels (B)<sup>12-15</sup> in the first three months of treatment (C).<sup>16</sup> However, testosterone does

not seem to have an effect on the sexual function of eugonadal males (B).<sup>12</sup> Long acting injectable testosterone has demonstrated greater tolerability and more physiological action (B),<sup>15</sup> while the oral form was not effective in improving sexual symptoms (A).<sup>17</sup>

Studies suggest a direct relationship between free testosterone and vasodilation of the *corpora cavernosa*. As such, testosterone therapy presents a synergic effect on patients with ADAM that have responded partially to phosphodiesterase inhibitors, significantly improving erectile dysfunction in such patients (B).<sup>12,13,18</sup> Ultimately, when erectile dysfunction does not respond to testosterone treatment, the combination of phosphodiesterase inhibitors should be considered (B).<sup>2</sup>

Not only testosterone but also DHEA has been considered an important androgen for adequate sexual function, although its effectiveness in improving sexual symptoms and erectile dysfunction has not been demonstrated (A).<sup>19</sup>

#### Recommendation

Testosterone replacement therapy is recommended for improving libido and sexual function only in patients with low testosterone levels. The use of testosterone is recommended for improving the libido and sexual function of patients with ADAM.

### WHAT IS THE ROLE OF ANDROGEN REPLACEMENT THERAPY (ART) TO IMPROVE MOOD, QUALITY OF LIFE AND COGNITIVE FUNCTIONS?

The influence of testosterone replacement therapy on the quality of life of older men has been widely evaluated. Although the majority of studies do not have good evidence, an important improvement on quality of life after testosterone replacement has been suggested in both hypogonadal and eugonadal men.

Comparing the quality of life of men with ADAM that use testosterone with those that do not, the improvement in the quality of life of the group using testosterone could be relative, i.e. determined by the decline in quality of life of the placebo group, suggesting a possible positive effect of testosterone on preventing the decline in quality of life with age (A).<sup>3</sup> Furthermore, the improvement of physical function and control and somatic and sexual symptoms with testosterone replacement improves the quality of life of patients with ADAM, and may constitute an important treatment strategy in old age (A)<sup>4</sup>(B).<sup>5</sup>

The effects of testosterone replacement on cognitive functions, mood and sense of wellbeing in men with ADAM are not yet clear. However, studies with excellent

evidence have demonstrated that regardless of the route of administration, dose or treatment time, testosterone replacement does not affect cognitive function, mood or quality of life in men with ADAM (A)<sup>20,21</sup> (B).<sup>22</sup>

#### Recommendation

Testosterone replacement improves mood and quality of life in men with ADAM; however, there is no evidence of a direct effect of testosterone over the above, or over cognitive function. It is strongly recommended not to use testosterone to specifically improve mood, quality of life or cognitive functions in men with ADAM.

### WHAT IS THE INFLUENCE OF ANDROGEN REPLACEMENT THERAPY (ART) ON THE METABOLISM OF CARBOHYDRATES AND LIPIDS?

Hyperinsulinemia and insulin resistance (IR) are antecedents of type 2 *diabetes mellitus* (T2DM) and metabolic syndrome, which in turn is characterized by IR associated with changes in lipid profile, among others. Type 2 diabetes is often associated with male hypogonadism, and it has also been suggested that testosterone replacement improves glycemic control as well as the body fat in patients with T2DM (B).<sup>23</sup>

Replacement therapy with injectable testosterone has been shown to be effective in improving insulin resistance and glycemic control with a significant reduction in fasting blood glucose and glycated hemoglobin (HbA1c) in hypogonadal men with type 2 diabetes (A)<sup>7</sup> or metabolic syndrome (C).<sup>16</sup> Similar efficacy has also been observed in the metabolic syndrome parameters, with a significant reduction in waist circumference, blood pressure, total cholesterol, LDL and triglycerides and an increase in HDL levels, albeit without changes in the dietary patterns (C).<sup>16</sup> An additional effect to that described above has been observed in the administration of long-acting testosterone. Patients with metabolic syndrome and ADAM achieved a dramatic reduction in the levels of insulin, leptin, HOMA-R and inflammatory markers such as IL-1 $\beta$ , TNF $\alpha$  and PCR (A).<sup>9</sup>

The association of testosterone with an aromatase inhibitor leads to a significant increase in the testosterone/estradiol ratio and thereby a significant reduction in triglyceride levels in such patients. Therefore, this combination may be particularly useful in patients with hypertriglyceridemia. However, the safety of the use of this association has not yet been established (A).<sup>24</sup>

Ultimately, the effects of testosterone on carbohydrate and lipid metabolism are still uncertain. Testosterone treatment in hypogonadal men with type 2 diabetes and/or

metabolic syndrome can lead to (yet unproven) benefits for their metabolic state (B).<sup>2</sup>

There is speculation about the role of the age-related decrease in DHEA on the metabolism of carbohydrates. The few studies that have addressed this issue suggest that DHEA has no effect on the metabolism of carbohydrates (B).<sup>25</sup>

### Recommendation

The effects and benefits of testosterone replacement on the metabolism of carbohydrates and lipids are still controversial. Testosterone replacement is recommended in men with ADAM and metabolic syndrome as an adjunctive to improve the metabolic profile of such patients.

## WHAT IS THE RISK OF ART IN RELATION TO EXACERBATING PROSTATE DISEASE?

Unfortunately, to date there is no consensus on the response pattern of PSA to testosterone therapy. It has been argued that a significant increase in PSA after beginning testosterone replacement can be a sign of prostate cancer. However, most studies do not support this argument.

Historically, TRT has been absolutely contraindicated in men with a suspected or confirmed diagnosis of prostate cancer. There is evidence that TRT can stimulate growth and aggravate the symptoms of prostate cancer in men with active disease.

TRT causes a mild increase in PSA in most patients without prostatic changes and such increase does not depend on patient age, mode of replacement, or baseline PSA levels and total free testosterone (B).<sup>26</sup> In intra-prostatic cancer patients with normalization of PSA after permanent brachytherapy or external beam radiation therapy who developed hypogonadism, testosterone treatment determined a slight increase in PSA with no signs of recurrence or progression of the cancer (C),<sup>27,28</sup> while in those submitted to radical prostatectomy, PSA levels did not change (B).<sup>29</sup> In all these studies, testosterone levels were maintained within the normal range. On the other hand, when serum testosterone levels are kept above the normal values in patients previously treated for prostate cancer, even with the association of 5- $\alpha$ -reductase inhibitors, PSA levels rise significantly (B).<sup>30</sup>

In patients who received curative treatment for low risk localized prostate cancer with the radical prostatectomy and/or radiotherapy, with no evidence of active disease, the risks and benefits of TRT should be assessed. There is no consensus on the moment for determining consolidated healing treatments with this intention in localized prostate can-

cer. Short-term studies with few patients suggest that after 1 year of treatment TRT can commence if the patient is cured.

The data available in the literature indicate that:

1. The incidence of prostate cancer in men with late-onset hypogonadism on TRT is no greater than the population in general (B);<sup>31</sup>
2. TRT in older men with late-onset hypogonadism seems to have a slight effect on prostate tissue (A);<sup>32</sup>
3. In patients with prostate cancer treated using radical prostatectomy, brachytherapy or radiotherapy, TRT can be used with caution, and patients should be constantly monitored (C);<sup>27,28</sup>
4. High doses of testosterone, even if associated with 5- $\alpha$ -reductase inhibitors, cause a significant increase in PSA (B).<sup>30</sup>

The greatest risk of prostate cancer has been observed in men with higher estrone levels (A);<sup>33</sup> however, studies with a higher number of patients should be conducted to confirm this observation.

### Recommendation

Maintaining testosterone at physiological levels increases PSA levels, but does not increase the incidence of prostate cancer. Men successfully treated for prostate cancer and diagnosed with hypogonadism are candidates for TRT after a prudent interval for observation, and there is no clinical or laboratory evidence of recurrence of the disease. The risks and benefits of TRT should be clearly understood by the patient and treatment should be carefully monitored. The safety data in this clinical situation are still limited. Maintaining physiological serum levels of testosterone and monitoring PSA in all patients on testosterone replacement is recommended.

## WHAT IS THE ROLE OF ART IN THE INCREASED RISK OF CARDIOVASCULAR DISEASE?

The effects of TRT on cardiovascular risk appear to be associated with the adverse effects on polycythemia, lipid profile and sleep apnea. On the other hand, TRT leads to a decrease in BMI and improves the lipid profile, providing cardiovascular benefit (B).<sup>31</sup> The maintenance of serum testosterone levels within the normal range does not lead to significant changes in hemoglobin and lipid profiles, decreasing the risk of developing polycythemia and consequently cardiovascular and vascular events (B).<sup>34,35</sup>

Hyperinsulinemia and insulin resistance (IR) are essential components of metabolic syndrome, which in turn is associated with an increased cardiovascular risk. TRT improves the components of metabolic syndrome

in hypogonadal patients with T2DM, reducing the cardiovascular risk (A).<sup>36</sup>

#### Recommendation

There is no evidence that TRT per se increases cardiovascular risk. It is recommendable to maintain serum testosterone levels within the normal range so that cardiovascular risk factors such as polycythemia and insulin resistance are minimized, thereby reducing overall cardiovascular risk.

### WHAT IS THE RISK OF POLYCYTHEMIA ON ART?

Secondary polycythemia is a major adverse event of TRT. Several authors have demonstrated its occurrence, and it is related to the maintenance of high serum levels of testosterone, regardless of the treatment time (B).<sup>31,34,35</sup> Therefore, the evidence available so far indicates that the maintenance of serum testosterone levels within the normal average does not lead to polycythemia (B).<sup>37</sup>

#### Recommendation

The appearance of polycythemia is directly related to supraphysiological serum testosterone levels. It is recommended to monitor hemoglobin and hematocrit in all patients on TRT and to maintain serum testosterone levels within the normal range to minimize the risk of polycythemia.

### WHAT IS THE HEPATOTOXICITY OF ART?

Hepatotoxicity due to TRT is a rare event limited almost exclusively to the use of oral 17 $\alpha$ -alkylated preparations such as fluoxymesterone and methyltestosterone, which are highly hepatotoxic and can cause the development of hepatocellular adenomas, liver carcinomas, cholestasis and hemorrhagic cysts of the liver (A).<sup>1</sup> The long term use of other testosterone preparations does not lead to a change in hepatic function among men with late-onset hypogonadism (B).<sup>31,35</sup>

#### Recommendation

17 $\alpha$ -alkylated oral preparations such as methyltestosterone and fluoxymesterone present hepatotoxicity. It is not recommended to monitor the liver function of patients on TRT with any other pharmaceutical form.

### WHAT IS THE EFFECT OF ART ON SLEEP APNEA? ARE THERE OTHER SIDE EFFECTS?

Testosterone replacement has been associated with the onset or worsening of sleep apnea in men treated with

high doses of testosterone (A).<sup>1</sup> The administration of testosterone in patients with sleep apnea and erectile dysfunction associated with low testosterone improves sexual symptoms and does not worsen sleep apnea (C).<sup>38</sup>

Gynecomastia is a benign, infrequent and generally reversible complication, a result of the aromatization of testosterone into estradiol in peripheral tissues. Infertility and decreased testicular volume are related to supraphysiological doses of testosterone. Sodium and water retention may occur during replacement and generally present clinical significance in patients with cardiac decompensation, hypertension or renal failure. Skin reactions such as erythema and itching are common with the use of patches. Intramuscular injections may cause local pain, lumps, rashes and boils. Acne, oily skin, increased body hair and skin "flushing" are benign and reversible complications that do not cause major concern (A).<sup>1</sup>

#### Recommendation

The side effects of TRT, such as worsening or onset of sleep apnea, gynecomastia, infertility, fluid retention and skin changes are directly related to supraphysiological levels of serum testosterone. It is strongly recommended to maintain serum testosterone levels within the average normal range to minimize the occurrence of these side effects.

### WHAT IS THE ROLE OF ART IN METABOLIC SYNDROME?

The maintenance of serum testosterone levels within the normal range leads to improvements in the markers of metabolic syndrome, such as waist circumference, and increased levels of HDL without causing polycythemia or changes in prostatic parameters. This improvement is not as significant when testosterone levels are maintained at the lower limit of normality (B).<sup>37</sup> TRT does not depend on the pharmaceutical form of testosterone used or the route of administration and is effective to improve metabolic syndrome parameters; when testosterone levels are maintained within a normal range, however, the improvement is more significant (B).<sup>39</sup> In T2DM patients, TRT reduces insulin resistance, improves glycemic control, and reduces visceral adiposity and total cholesterol, which are all components of metabolic syndrome (A).<sup>36</sup>

The beneficial effects of ART on metabolic syndrome components appear to be specific to testosterone, given that chronic replacement with DHEA does not improve the secretion or action of insulin and postprandial glycemia in women and elderly men (B).<sup>40</sup>

### Recommendation

There is strong evidence that testosterone replacement improves the parameters of metabolic syndrome, especially if serum levels are maintained within normal limits. We recommend maintaining serum testosterone levels within a normal range to aid in the treatment of metabolic syndrome.

### HOW SHOULD ART BE ADMINISTERED ORALLY?

Oral testosterone formulations have been developed to replace injectable forms; however, some disadvantages have been noted, such as variable absorption, low bioavailability due to liver metabolism and the need for 2 to 3 daily doses (**D**).<sup>41</sup> Moreover, 17 $\alpha$ -alkylated derivatives are hepatotoxic (**A**)<sup>1</sup> (**D**)<sup>41</sup> and have already been withdrawn from the American market (**A**).<sup>19</sup> Oral testosterone undecanoate (OTU), the only available oral formulation, is preferably absorbed in chylomicrons, avoiding the primary hepatic passage (**D**)<sup>41</sup> and significantly reducing hepatotoxicity (**A**).<sup>17</sup> Although most of the studies were flawed due to the small number of participants or the variability of the dose used, the effectiveness of oral ART is questionable. Several authors have shown that the OTU, even at appropriate doses (160 mg/day) was not effective in improving sexual function, wellbeing, sleep disturbances, cognitive function, mood and quality of life in men with ADAM (**A**).<sup>17,19,20</sup> The manufacturer's recommendation is for OTU to be taken during meals, yet there is variability in absorption depending on the composition of the patient's diet (**A**).<sup>19</sup>

DHEA has been proposed as an alternative oral ART, but the results are controversial. Morales et al.<sup>19</sup> demonstrated that the ingestion of 50 mg of DHEA orally twice a day, although leading to satisfactory serum levels did not improve the sexual function of men with ADAM (**A**).<sup>19</sup> On the other hand, replacement with lower doses of DHEA (75 mg/day) improved insulin resistance in the individuals treated (**B**).<sup>42</sup>

Another way to release testosterone orally is oral mucosa patches which contain 30 mg of testosterone that should be administered twice daily. In general, studies show that this form of ART is capable of maintaining physiological levels of serum testosterone, is safe and well tolerated, and is an interesting option for ART in hypogonadal men (**D**)<sup>41</sup> (**B**).<sup>43,44</sup>

The underreported sublingual form of testosterone administration should be used at a dose of 2.5 mg or 5 mg, 3 times a day. It is rapidly absorbed and metabolized, and it does not lead to a sustained increase in serum levels of dihydrotestosterone (DHT) and estradiol (**D**).<sup>41</sup>

### Recommendation

Oral testosterone undecanoate does not present hepatotoxicity; however, it has proved ineffective in maintaining adequate serum testosterone levels, and has variable absorption between individuals. It is strongly recommended NOT to use oral formulations of testosterone and other androgens as an alternative to TRT.

### HOW SHOULD ART BE ADMINISTERED TRANSDERMALLY?

Transdermal administration of ART includes patches, cutaneous gels and cutaneous solutions.

The patches may be non-scrotal or scrotal, which are thinner and have more effective testosterone absorption than the non-scrotal version. The first presentation of transdermal testosterone was the scrotal patch with release of 4 or 6 mg testosterone/day. It should be applied once daily on depilated scrotal skin (**D**).<sup>41</sup> The most commonly used patches are non-scrotal, releasing 5 mg/day of testosterone and should be applied once a day on clean and dry glabrous skin (**B**).<sup>43</sup>

Due to the large number of patches on the international market from different manufacturers, in the opinions of the authors, the tolerability of patients is quite variable due to local adverse effects. They are considered large and uncomfortable to use, and some formulations cause local reactions and exhibit low adhesion that ends up causing low acceptability by patients (**B**).<sup>43</sup> There are reports of patients who have discontinued treatment due to allergic reactions at the application site, even when using a local corticosteroid ointment (**B**).<sup>44</sup>

On the other hand, the authors are unanimous regarding the efficacy and safety of this type of ART. The transdermal patches available provide physiological and constant levels of serum testosterone, and mimic the circadian rhythm. At a dose of 5 to 7.5 mg/day, changing patches every 48 hours, they are capable of producing a significant improvement in symptoms and quality of life of patients with ADAM (**A**)<sup>8</sup> (**B**).<sup>45-47</sup> With respect to security, Raynaud et al.<sup>44,47</sup> reported that the use of transdermal patches showed no negative impact on the hematocrit and lipid profile of patients (**B**),<sup>45</sup> and does not contaminate other people or the environment (**B**).<sup>47</sup>

Many patients prefer transdermal gels or solutions as they are easy to apply, substantially free of local reactions and do not require injections (**D**).<sup>41</sup> Testosterone gel formulations available on the health market are available in the concentration of 1% as "pumps", so that each "puff" releases 1.25 g of product; individual 2.5 g and 5 g packages or single dose tubes containing 5 g of the product.

The recommended dose for starting treatment is 5 g/day, which can be increased up to 10 g/day (D).<sup>48</sup>

Testosterone gel should be applied in the morning on dry skin on the shoulders, arms or abdomen. Patients should wash hands well after application and let the application site dry before putting on clothes. It is recommended to wait 4 hours after application to bathe or swim. The application site should be washed with soap and water if there is direct contact with another person (D).<sup>48</sup>

Testosterone gels at the recommended doses are able to restore the physiological serum testosterone levels but they do not mimic the circadian rhythm (B)<sup>46</sup> and promote a significant improvement of sexual symptoms and quality of life for patients with ADAM (B).<sup>13</sup> Even at higher doses (60 mg) applied once daily they promote testosterone levels within the normal range in most patients (B).<sup>49</sup>

The association of this type of ART with sildenafil at the maximum dose (100 mg/day) improves erectile dysfunction in hypogonadal men who do not respond to treatment with testosterone alone (B),<sup>50</sup> or sildenafil alone (B).<sup>49</sup>

Transdermal testosterone solution at 2% for axillary use is a new treatment option with characteristics similar to those described for gels (B).<sup>51</sup>

A less frequently used form of transdermal ART is the use of dihydrotestosterone gel. Few studies are available for this type of ART. The dose of DHT gel is 70 mg/day for 3 months in patients with ADAM proved to be safe, but with limited effect on physical and cognitive functions. A greater number of long-term studies with a greater number of patients are needed to confirm the safety and efficacy of DHT as a treatment option for ART (A).<sup>52</sup>

#### Recommendation

There is strong evidence that transdermal testosterone replacement (patches, gels or solution) is safe and effective in addition to being the most physiological. Patches, in turn, are capable of mimicking the circadian rhythm of testosterone secretion; however, these pharmaceutical forms are not available in our country. The use of transdermal TRT is recommended for being the most physiological.

### IS THERE A DIFFERENCE BETWEEN THE COMMERCIAL GEL AND COMPOUND GEL?

There are no scientific studies comparing commercial gels and compound ones. Only two studies have compared gels that are produced in two different countries that are not widely available in the global market. The ointment produced in Japan was used on 50 patients with ADAM at a dose of 3 mg twice daily on the skin of the scrotum for 12 weeks and caused a physiological increase in total

and free testosterone with no severe adverse effects (B).<sup>53</sup> The gel produced in Germany was applied both on scrotal and non-scrotal skin and removed after 10 minutes in hypogonadal men. There was better tolerability than the commercial gels, less chance of interpersonal transfer due to early removal of the gel and an effective increase in testosterone levels (B).<sup>54</sup>

#### Recommendation

Studies with a good level of evidence using noncommercial testosterone gel are still scarce. The use of a testosterone gel preparation without proven efficacy and safety is not recommended.

### HOW SHOULD ART BE ADMINISTERED USING SUBCUTANEOUS IMPLANTS?

Subcutaneous implants are composed of 1,200 mg of crystallized testosterone, are generally more accepted by patients, but require a surgical procedure and if not performed by experienced physicians may have high rates of extrusion (B).<sup>43</sup> The implants are changed every 3-6 months and are considered safe in long-term studies (B).<sup>34</sup> Experience with this type of ART is still limited in the literature.

#### Recommendation

Studies with a good level of evidence for this form of TRT are scarce and this pharmaceutical form is not available in our country. We recommend not using subcutaneous testosterone implants until a larger number of studies on safety and efficacy can be found, as the extrusion rate appears to be high.

### HOW SHOULD INJECTABLE ART BE ADMINISTERED?

Injectable testosterone preparations have been widely used for many years. They consist of various testosterone esters, combined or otherwise, namely, propionate, phenylpropionate, enanthate, cypionate, decanoate, isocaproate and undecanoate (D).<sup>41</sup> All formulations are available in Brazil, except those containing testosterone enanthate (B).<sup>55</sup> All injections with testosterone esters have short action, except for testosterone undecanoate depot (TUD).

The short acting formulations must be injected every 14-21 days while the long acting ones should be applied every 6 weeks at the start of the treatment and every 12 weeks thereafter (D)<sup>41</sup> (B).<sup>55</sup> Replacement therapy using short acting testosterone for a short period of time has proven effective and safe, improving sexual function in patients without increasing hematocrit or PSA (D)<sup>41</sup> (B).<sup>55,56</sup>

In relation to TUD, in order to achieve adequate serum levels, the second injection should be given after 6 to 10 weeks, with the interval subsequently extended up to 10-14 weeks (B).<sup>57</sup> It is recommended to apply the second injection after 6 weeks and then one injection every 12 weeks (B)<sup>15,58,59</sup> (C).<sup>16</sup> It is usually well tolerated and changes in the actions and side effects are more frequently observed in obese patients (B).<sup>57</sup>

There are two presentations of TUD – the formulation available in the USA contains 750 mg of TUD, maintains serum testosterone levels within the normal range during an interval of 10 weeks between doses and has proven to be safe and effective (B).<sup>60</sup> 1000 mg TUD is available in Europe and South America, including Brazil. Its pharmacokinetics enables one injection every 12 weeks to be able to maintain physiological levels of serum testosterone without causing peaks above normal (B).<sup>55</sup>

### Recommendation

Although not the most physiological, the short acting injectable forms have proven safe and effective over time, but with the disadvantage of fortnightly application. Besides providing physiological levels of testosterone, the pharmacokinetics of TUD enables quarterly applications, but with the disadvantage of having a high cost. Among the available injectable forms, the use of TUD to maintain physiological levels of testosterone is recommended in order to minimize side effects with fewer injections.

## ARE THERE COMPARATIVE STUDIES BETWEEN THEM? WHAT IS THE BEST FORM OF ART?

The criterion to assess efficacy of ART is that testosterone levels are maintained within normal limits during the 24 hour interval between two applications (WHO, 1992). The various testosterone formulations differ mainly in relation to the route of administration and the pharmacokinetics of the components, causing variability in their effectiveness.

Several authors have carried out comparative studies between them. In men with ADAM and metabolic syndrome, treatment with TUD demonstrated greater effect on sexual symptoms and metabolic syndrome parameters than testosterone gel (A)<sup>36</sup> (B),<sup>38</sup> while the safety parameters were similar in both modalities (B).<sup>38</sup>

A 30 weeks follow-up of patients who used short acting TUD or testosterone enanthate showed that the effects of the two formulations were similar, although treatment with TUD requires only four injections per year to maintain testosterone levels within the physiological range. Polycythemia was not observed in patients who used TUD (B).<sup>15</sup>

The comparison of the pharmacokinetics and tolerability of oral patches and non-scrotal skin patches showed that the oral system promotes physiologic levels of testosterone at a higher percentage of the day than conventional skin patch systems (B).<sup>43</sup>

A comparative study between the ART and skin patches at the maximum dose (4.8 mg every 48 hours – 2 patches) and short acting testosterone (250 mg every 3 weeks) showed that the percentage of patients who maintained stable and physiological levels of testosterone was higher in those using patches than in patients who used injectable testosterone, with high variability in the testosterone levels (B).<sup>44</sup>

The effects of the three injectable formulations available in Brazil (two with short acting esters and one with TUD) were compared and it was found that the three formulations are effective in raising testosterone levels and clinically improving hypogonadal patients, with TUD – even though, more expensive – being clinically and laboratorially more effective. The three options were shown to be safe without significantly increasing hematocrit, hemoglobin and PSA (B).<sup>55</sup>

The treatment of hypogonadal patients with short acting injectable testosterone at doses of 100-200 mg/week who were subsequently submitted to treatment with testosterone gel at a dose of 5-10g gel/day demonstrated that testosterone gel produced stable concentrations of testosterone and improved the quality of life of patients compared to injectable testosterone (B).<sup>61</sup>

The usual dose of testosterone gel determined physiological levels of serum testosterone at physiological levels that were not significantly changed after association of any dose of oral testosterone (B).<sup>62</sup>

Therefore, the comparative analysis between the main types of ART has shown that all are safe, and transdermal forms and TUD are the most physiological.

### Recommendation

The comparative analysis between the main types of ART has shown that all are safe, and transdermal forms and TUD are the most physiological. The use of TUD or testosterone gel is recommended, whenever possible, for ART in hypogonadal patients.

## WHAT IS THE ROLE OF PROLONGED ACTION TESTOSTERONE?

There are two formulations of long acting testosterone undecanoate, one presented in 750 mg vials, available in the US, and another with 1000 mg vials, available in Europe and South America. Both are well tolerated by patients, are able

to maintain physiological and stable levels of serum testosterone and DHT (**B**)<sup>59</sup> and have similar effectiveness and safety as other injectable forms (**B**)<sup>58,63</sup> (**D**).<sup>64</sup> The advantage of TUD is that with only 4-5 injections per year testosterone levels can be maintained at physiological levels (**B**).<sup>15</sup>

TUD appears to have a role in the treatment of metabolic syndrome. A follow-up of patients with metabolic syndrome and ADAM using TUD for a period of one year showed that testosterone levels were restored to the normal average value. There was a significant improvement in sexual symptoms, metabolic syndrome parameters and body composition. There was no change in PSA, blood glucose and liver function, and the levels of hemoglobin and hematocrit did not exceed the upper limit of a normal range (**A**)<sup>36</sup> (**B**)<sup>38</sup> (**C**).<sup>16</sup>

The increase in blood pressure, hematocrit > 50% and worsening lipid profile that may occur in a small number of patients were related to the number of CAG repeats of the androgen receptor and the presence of obesity (**B**).<sup>57</sup> ART with long acting TU proved to be safe for a period of 24 months of treatment.

#### Recommendation

The main role of long acting testosterone is maintenance of physiological serum testosterone levels with a lower number of applications and consequently lower rate of side effects.

### IS THERE A DIFFERENCE IN ABSORPTION BETWEEN THE MANY PHARMACOLOGICAL PREPARATIONS?

Each formulation has a distinct characteristic, depending on the presentation, dose and pharmacokinetics. The testosterone esters used in short acting injectable formulations are derived from fatty acids and depend on the esters being released from the oily vehicle and the hydrolysis of these esters in order to release of testosterone into the circulation. The pharmacokinetics are determined in part by the size of the side chain, hence the wide variation in the use of different esters modulates the level of circulating testosterone (**D**).<sup>41</sup>

The testosterone levels obtained with short acting injectable forms are unstable (**B**),<sup>55,61</sup> whereas long acting injectable forms provide more stable levels.

In the oral formulations, absorption is variable and bioavailability is generally poor due to the effect of first passing through the liver. Oral testosterone undecanoate is preferentially absorbed by chylomicrons, avoiding the liver. However, the testosterone level is sub-optimal and it must be taken various times per day (**D**).<sup>41</sup>

The oral mucosa patches and sublingual formulation are not often used. The first seems to have a good absorption similar to that of gels, but a shorter half-life, requiring use twice per day (**B**).<sup>43</sup> Transdermal patches are presented in formulations that vary in size and thus the dose of testosterone. Studies indicate that absorption is efficient and reaches equilibrium in 48 hours (**B**).<sup>44</sup> The absorption of scrotal patches is more efficient because the skin is thinner and increased production of DHT occurs because the amount of 5 alpha reductase in that region is higher (**D**).<sup>41</sup> The evening application of the patch produces serum testosterone mimicking the circadian rhythm of healthy men, while the application of the gel in the morning produces physiological and stable serum testosterone levels (**B**),<sup>15,46,55,61</sup> which shows the different absorption mechanisms between the two formulations.

#### Recommendation

The differences in absorption between the various pharmaceutical forms depend on the presentation, dose and pharmacokinetics. Testosterone levels obtained by short acting injectable forms and oral forms are more unstable and less physiological. On the other hand, the levels obtained by means of injection and for long acting transdermal forms are stable and physiological. The only pharmaceutical form that mimics the circadian rhythm is that of scrotal patch. The preferential use of the long acting injectable form or transdermal forms is recommended for ART.

### WHAT ARE THE CONTRAINDICATIONS FOR ART?

An increased risk of cardiovascular events has been observed in elderly patients with ADAM associated with other chronic diseases.

The administration of testosterone is contraindicated in men with prostate or breast cancer, in men with palpable prostate nodules or PSA greater than 4 ng/mL or 3 ng/mL in high risk patients (**D**).<sup>41,48</sup>

ART is recommended to be applied with caution in men with benign prostate hypertrophy and mild or moderate urinary symptoms, while men with severe urinary symptoms should undergo urologic evaluation before starting treatment.

Testosterone should not be used in men with hematocrit > 50% or patients with grade III or IV CHF. Men with moderate or severe obstructive sleep apnea should be evaluated by a specialist before starting ART (**D**).<sup>48</sup>

## Recommendation

There are few studies with high levels of evidence in relation to the contraindications of testosterone replacement. It is weakly recommendable to not use testosterone in patients with prostate or breast cancer with PSA > 4 ng/mL or 3 ng/mL in high risk patients or those with palpable prostate nodule, hematocrit greater than 50% or in patients with grade II or IV CHF.

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# Spontaneous rupture of renal pelvis secondary to ureteral obstruction by urothelial tumor

## RUPTURA ESPONTÂNEA DE PELVE RENAL SECUNDÁRIA À OBSTRUÇÃO URETERAL POR TUMOR UROTELIAL

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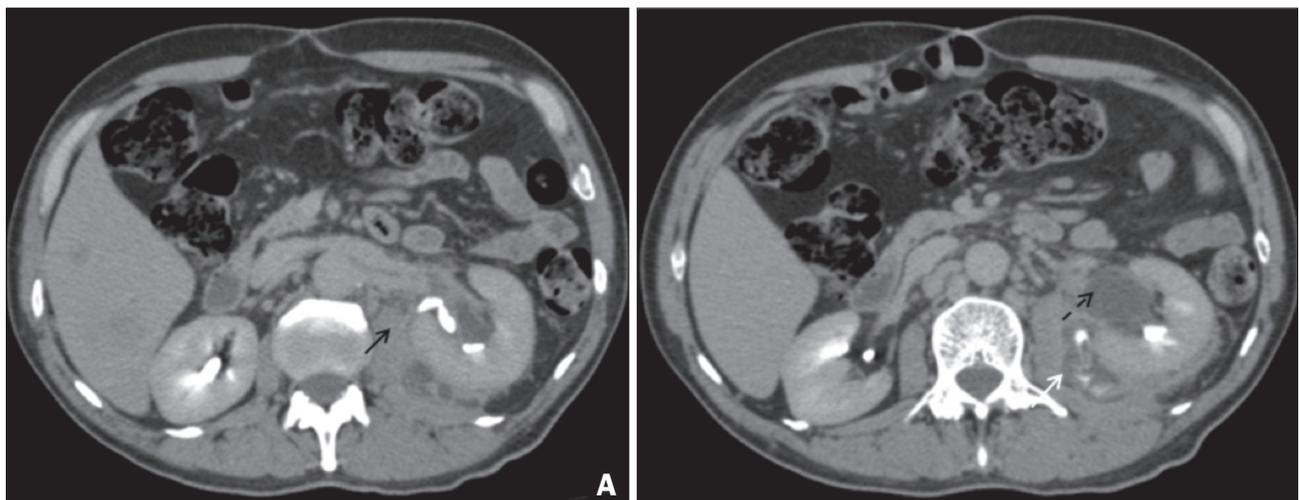
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### INTRODUCTION

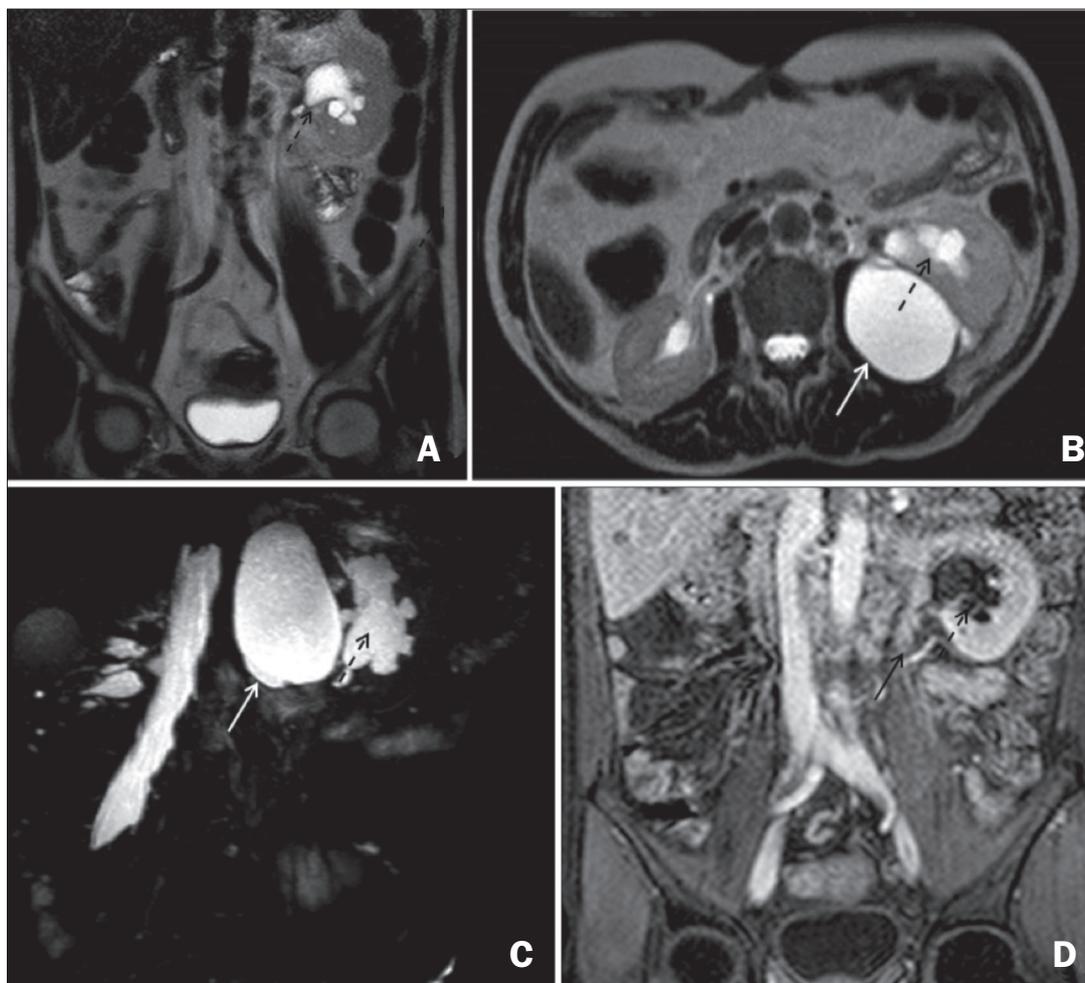
Partial spontaneous rupture of the upper urinary tract is rare and usually associated with nephrolithiasis. Other reported causes, apart from instrumentation and trauma, involve obstructive ureteral tumor in the pelvic cavity, retroperitoneal fibrosis, fluid overload, and pregnancy. We report a case of spontaneous rupture of renal pelvis secondary to ureteral obstruction caused by urothelial tumor, clinically suspected and evaluated by CT scans and MRIs, discussing the relevant findings for diagnosis.

### CASE REPORT

Male patient, 55 years, with a clinical picture of macroscopic hematuria and insidious lower back pain similar to cramps for about six months, which became stronger in recent months. The patient reports a fever, not measured. Denies trauma, previous surgery, history of urolithiasis, other complaints, and past illnesses. Former smoker (22 packs/year, having quit smoking for eight years). On physical examination, the patient showed good general health, being thin (body mass index of 17.2 Kg/m<sup>2</sup>), pallid (1+/4),



**FIGURES 1A AND 1B** Computed tomography, contrast-enhanced axial sections; excretory phase shows irregular parietal thickening of the left ureteropelvic junction, causing ureteral obstruction (black arrow) and moderate upstream pyelocaliceal dilatation (dashed arrow). Rupture of the renal pelvis with contrast extravasation and formation of posterior perirenal urinoma is also observed (white arrow).



**FIGURES 2A, 2B, 2C AND 2D** MRI with T2-weighted images, coronal (2A) and axial (2B), three-dimensional MR urography (2C) and post-contrast T1 image (2D) revealing vascularized tumoral thickening of the proximal left ureter (black arrow), causing ureteral obstruction and moderate pyelocaliceal upstream dilation (dashed arrow). Associated rupture of the renal pelvis with contrast extravasation and formation of posterior perirenal urinoma also observed (white arrow), displacing the kidney anterolaterally.

hypohydrated (2+/4), acyanotic, anicteric, eupneic and afebrile. Abdomen with bowel sounds present and preserved, slightly painful on palpation in the left flank and iliac fossa. Painful lumbar fist percussion on the left.

Based on the clinical picture, we requested a contrasted multi-slice computed tomography (Figures 1A and 1B) and subsequent complementation with MR urography - Uro-MRI (Figures 2A, 2B, 2C and 2D). Vascularized tumoral thickening of the proximal left ureter evident, causing ureteral obstruction and moderate pyelocaliceal upstream dilation. Associated rupture of the renal pelvis with contrast extravasation and formation of posterior perirenal urinoma is also observed, displacing the kidney anterolaterally. Imaging diagnosis (with subsequent histopathological confirmation) led to the conclusion that it was a case of spon-

taneous rupture of renal pelvis and formation of urinoma secondary to ureteral obstruction due to urothelial tumor.

## DISCUSSION

In the case described, the spontaneous rupture of renal pelvis was caused by urothelial tumor. The rupture diagnosis can be clinically suspected and confirmed by imaging. The clinical picture includes macro or microscopic hematuria (75%), back pain (18%), dysuria (6%) and less frequently palpable mass, decreased appetite, weight loss, and may sometimes be asymptomatic.<sup>1-4</sup>

Urothelial tumors can affect any part of the urinary tract is relatively rare in the upper urinary tract (approximately 1% of all urothelial tumors), most frequently affecting patients in the sixth and seventh decades of life. The

histological subtypes include transitional cell carcinoma (TCC) (90%), squamous cell carcinoma (9%), mucinous adenocarcinoma (less than 1%), sarcomas, undifferentiated tumors and benign tumors (mesodermal inverted papilloma, and fibroepithelial polyp). Risk factors involve smoking, prolonged exposure to dyes such as aniline, petrochemical agents and tar, analgesic abuse (especially phenacetin), Balkan nephropathy, as well as factors that promote urinary stasis, as horseshoe kidneys. The use of cyclophosphamide, in turn, increases the risk of high-grade urothelial tumors. Chronic infection and calculi may also be associated with squamous cell carcinoma and mucinous adenocarcinoma. Schistosomiasis can be associated with the squamous cell carcinoma, and also seems to be associated with a greater degree of epigenetic changes in the epithelium of the genitourinary tract.<sup>4-6</sup>

There is a clear need in patients with upper urinary tract tumors for imaging investigation of the entire urinary tract, due to possible synchronous bladder cancer in 2-4% of patients. Furthermore, the need for follow-up is well established, as 40-50% of patients with TCC will develop metachronous tumours involving the lower urinary tract.<sup>3-5</sup>

Urotomography (Uro-CT) performed with equipment with multiple rows of detectors (MDCT) is being increasingly used for evaluation of synchronous and metachronous tumors in the upper urinary tract and primary evaluation of hematuria. Imaging studies are also used to differentiate tumors and benign urothelial changes which might not require additional invasive assessment such as ureteroscopy and retrograde pyelography.<sup>7-9</sup> The differential diagnosis of tumors in the upper urinary tract includes nephrolithiasis, blood clot, infection, tuberculosis, ectopic papilla, endometriosis and malakoplakia. Factors that help to reach a correct diagnosis include knowledge of the location, lesion density and pattern of impregnation, pericalicinal/periureteral opacification associated or not, and multiplicity of lesions. In the unenhanced phase of Uro-CT, TCCs are discreetly hyperdense compared to urine (15-30HU), unlike clots and stones (with respective densities at 40-80 HU and above 200HU). Since most of them are hypovascularized, they are discreetly impregnated by contrast (increase of 40-70HU), and to a lesser intensity than normal renal parenchyma, appearing in the excretory phase of the examination as fixed filling defects.<sup>5</sup> In addition to technological improvements in MDCT, refinements in the tests' radiological orientation have probably contributed to increase the capacity to detect urothelial abnormalities. Different techniques have been used, such as abdominal compression, administration of intravenous saline solution, diuretics

or both, "log-rolling" (asking patients to roll 360°) prior to excretory phase to maximize opacification and distention of the urinary tract.

On MRI, TCCs can appear hypointense or isointense compared to the renal parenchyma on T1- and T2-weighted sequences, making it necessary to use paramagnetic contrast agents in non-dilated urinary tract, being the TCCs less contrasted than the renal parenchyma. In patients with impaired renal function, static MR urography can help detect tumors of the upper urinary tract, especially in obstructed kidneys, since TCCs are usually hypointense compared to urine on T2-weighted images, which facilitates their detection when associated to hydronephrosis. The use of diffusion-weighted imaging (DWI) sequences associated with conventional T1- and T2-weighted sequences increases the accuracy and sensitivity of Uro-MRI.<sup>10,11</sup>

## CONCLUSION

Although rare, spontaneous rupture of renal pelvis secondary to ureteral obstruction caused by urothelial tumor may be suspected clinically, and the detailed radiological analysis of tomographic images and MRI-guided sequences, including Uro-MRI, is of great importance for both diagnosis and follow-up of these patients.

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# Stress in nurses in Intensive Care Units

## ESTRESSE EM ENFERMEIROS DE UNIDADES DE TERAPIA INTENSIVA

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### OBJECTIVE

To assess the level of stress, and associated activities in nurses working in the Intensive Care Unit.

### METHODS

Prospective cross-sectional study to answer the following questions: is the stress level of nurses working in ICU high? Is there a relationship between stress and working conditions? Which of the activities of nurses generate more stress?

The population consisted of 71 nurses working in ICUs, distributed in 6 hospitals. Data collection was performed using the Bianchi questionnaire,<sup>1</sup> based on the 51-item total stress score for nurses, including the relationship with other units and superiors (A), activities related to the unit's proper functioning (B), staff administration (C), nursing care provided to the patient (D), unit coordination (E) and working conditions (F). The total score value has a variation of 51 points (when the nurse classifies all activities as stressful) and 357 points (when the nurse classifies all activities as very stressful), resulting in the average value between 1 and 7. Levels obtained were classified into low (equal to or less than 3), moderate (3.1 to 5.9) and high (equal to or greater than 6) levels of stress.

### RESULTS

Regarding general data, the majority were female (74.64%), aged 31-40 years (46.67%), married (53.5%), with children (59.15%). 61.97% of these nurses do not have another job and 60.56% work 12-hour shifts. Regarding training time, 38.02% had work experience of two to five years and 84.5% of respondents had graduate degree diplomas.

The average stress of these nurses reached a score of 3.87, which according to the reference values is equivalent to a moderate stress level. The highest stress score was 4.27, and the lowest stress score of 3.36. There was no significant difference between hospitals ( $p = 0.65$ ).

In terms of score distribution among hospitals, 49 nurses (69.01%) show moderate levels, 20 nurses (28.16%) have low levels, and 2 nurses (2.81%) have high levels of stress.

There was no significant difference in the level of stress in relation to gender, age, dual employment, working hours, training time and graduate degree.

Regarding domains, personnel administration (C) showed a higher stress score. Performing activities with minimal time available was the most stressful activity (F). Nursing care provided to the patient (D) showed a higher number of stress-generating activities.

### CONCLUSION

Regardless of the results of this study, it is important to establish parameters to systematically measure the stress level of health professionals involved in care or administrative activities. The stress level of nurses in this study or in other samples may indicate specific areas to receive interventions aiming at improving performance and quality of patient care.

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# Spatial distribution of C-sections within the state of São Paulo

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## SUMMARY

**Objective:** to identify spacial patterns for cesarean deliveries per microregion in the state of São Paulo.

**Methods:** this is an ecological and exploratory study with data on live births occurred between 2003 and 2007 in 63 microregions in the state of São Paulo. Variables analyzed included cesarean delivery rates, teenage mothers, mothers with high levels of education and who had at least seven prenatal consultations. Moran's index (I), a measure of spatial autocorrelation of rates related to the variables described above and which identifies the presence of spatial clusters, was calculated. The distributions of the variables' rates in this study were visualized using thematic maps. The Moran map was used to identify microregions with high priority need for attention. Pearson correlation coefficients among the variables were also obtained.

**Results:** there were 3,045,293 births, being 1,636,009 (53.7 %) cesarean deliveries. It was possible to identify spatial clusters of C-sections ( $I = 0.58$  and  $p < 0.01$ ) in the microregions located on the north and northwest of the state of São Paulo, as well as in Guaratinguetá; the values found for Moran index were,  $I = 0.32$ ,  $I = 0.30$  and  $I = 0.24$ , for the rates of teenage mothers, schooling and number of consultations, respectively, being all significant results ( $p < 0.01$ ). Micro-regions with high-priority need for attention were identified. Cesarean rates were significantly correlated with high rates of maternal education and number of prenatal consultations.

**Conclusion:** the identification of these microregion clusters with high rates of cesarean delivery allows health managers to implement policies in order to minimize these rates.

**Keywords:** spatial distribution of the population, public health, C-section, maternal age, maternal education, geographic information systems.

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## INTRODUCTION

Currently, Brazil has an overall C-section rate of 32%, reaching 90% in some private clinics.<sup>1</sup> In the state of São Paulo, the rate of C-sections amounts to 32.9% in the public setting and 80.4% in private setting.<sup>2</sup> Compared to spontaneous vaginal delivery, cesarean section is associated with an increased risk of infections, occasional need for blood transfusion, pneumonia, cardiopulmonary complications, thromboembolism and gastrointestinal disorders in women giving birth.<sup>1,3-6</sup> In addition, the risk of hospital readmission within sixty days after surgery is higher than that seen after spontaneous vaginal delivery.<sup>5</sup>

A recent review showed that the rates of cesarean delivery have increased in recent years in European countries, and the rates around the world have been between 13.5% and 39.2% of births.<sup>7</sup>

Geoprocessing is becoming an important tool in the field of Public Health, as it allows an overview of a particular problem. This technique was used in determining areas for malaria control,<sup>8</sup> in the spread of the AIDS epidemic,<sup>9</sup> and in the study of birth profiles in Vale do Paraíba.<sup>10</sup>

One of its applications encompasses the identification of spatial clusters defined as any cluster of events

that is not merely casual and whose identification is the focus of research in spatial statistics.

With the development of these maps, we seek to examine whether the distribution of these events actually follows a pattern in terms of space or if it is a random event.

The objective of this study was to identify spatial clusters of cesarean section rates in microregions of the state of São Paulo.

## METHODS

This is a study of ecological and exploratory design, in which secondary data from live births were used; the information was gathered from the Datasus portal and refers to microregions within the state of São Paulo in the period from January 1, 2003 to December 31, 2007. Data were georeferenced according to the place of residence of the mother. These data were analyzed using TerraView 4.0.0. software program, made available by the National Institute for Space Research - INPE ([www.dpi.inpe.br/terraview/](http://www.dpi.inpe.br/terraview/)). The proportions of cesarean deliveries were calculated according to the following groups: mothers aged below 20 years, mothers with formal education above eight years (high school and above), and mothers who had seven or more prenatal consultations. These proportions were obtained in percentages and compared to the total number of live births.

63 microregions that make up the state of São Paulo and have an approximate population of 41 million inhabitants were analyzed.

The spatial statistics used a georeferenced database of the microregions, and a data analysis technique divided by area in order to obtain the Global Moran's index (I). The equation that expresses this index takes into account the number of areas (microregions), the weights of the neighborhoods, the average incidence rate of cesarean section for each microregion in the periods studied and the mean values for the entire study area.

The Moran's index is a global measure of spatial autocorrelation; spatial autocorrelation measures the association of values of a single variable *Y* within any specific area *i* with the values of the same variable *Y*, however measured for an area neighboring *i*. That is, the index measures the extent to which the value of a variable in an area is associated with the same variable in neighboring areas. We can say that autocorrelation measures the level of spatial interdependence between the variables and the strength of the relation determining whether that is a random distribution or not. Its value is contained in the [-1; 1] interval. The closer to 1, the more similar the areas compared to each other, whereas the closer to -1, the least similar these areas would be from each other.

These indices were calculated for all areas. Thematic maps that allow visual identification of the distribution of these events in the microregions were prepared.

A Moran map of C-section rates was created; the map shows areas of high priority for possible intervention. The Moran map is a two-dimensional representation of the Moran scatterplot where each polygon is displayed, indicating its quadrant in the scattering diagram. In this map, the microregions located in Q1 require special attention in order to reduce the rates of the studied outcome, which in our case is the rate of cesarean deliveries.

The Pearson correlation coefficients between C-section rates and other variables were estimated.

Tables with the coefficients of global Moran and Pearson correlation were built. The variables were expressed as percentages in the tables, with mean, minimum and maximum values.

As this is an ecological study using secondary data obtained from the network, identifying the subject is not possible, and thus approval by the Research Ethics Committee was not required.

## RESULTS

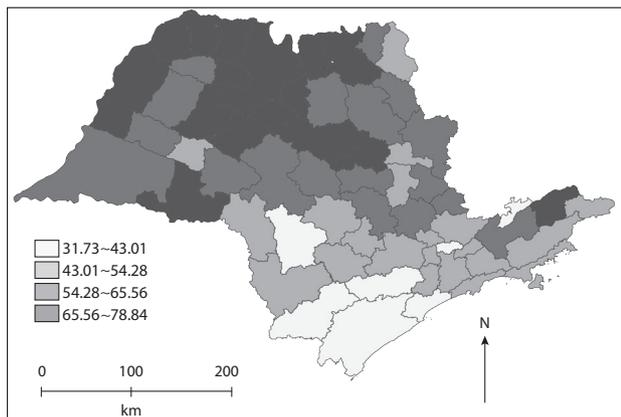
During the study period, there were 3,045,293 live births, of which 1,636,009 (53.7%) were delivered by cesarean section. The percentages of other variables, along with their mean, minimum and maximum values are shown in Table 1. The high mean value of the proportion of cesarean deliveries is clearly observed.

**TABLE 1** Mean, minimum and maximum (Min - Max) values, and respective standard deviations (SD) of rates per 100 live births, delivered by C-section; mothers with high level of education; mothers aged less than 20 years (adolescents); and mothers who had seven or more prenatal consultations, by microregion in the state of São Paulo, from 2003 to 2007

	Mean (SD)	Min- Max
Cesarean delivery	57.0 (10.8)	31.7 - 76.8
Adolescent mothers	19.5 (2.3)	14.6 - 25.0
Mothers with high level of education	70.8 (7.5)	42.4 - 72.8
Mothers who had seven or more prenatal consultations	74.1 (10.2)	39.4 - 93.7

The Moran index (I) was positive and significant for all variables studied, demonstrating the presence of spatial clusters for all determinants.

The spatial distribution of cesarean deliveries, represented here by rates per 100 live births, by microregion in the state of São Paulo, from 2003 to 2007, is shown in Figure 1. The presence of high rates of cesarean sections in the north and northwest part of the state is evident, with spatial clusters toward the border of the states of Minas Gerais, Mato Grosso do Sul and northern Paraná, as well as in the microregion of Guaratinguetá, within Vale do Paraíba. Lower rates were found to the south of the state near the border of Paraná and in the microregions of Avaré, Franco da Rocha, and Campos do Jordão. Moran's index was  $I = 0.58$  ( $p < 0.01$ ).



**FIGURE 1** Spatial distribution of rates of cesarean delivery, in percentages, by microregion in the state of São Paulo, 2003-2007.

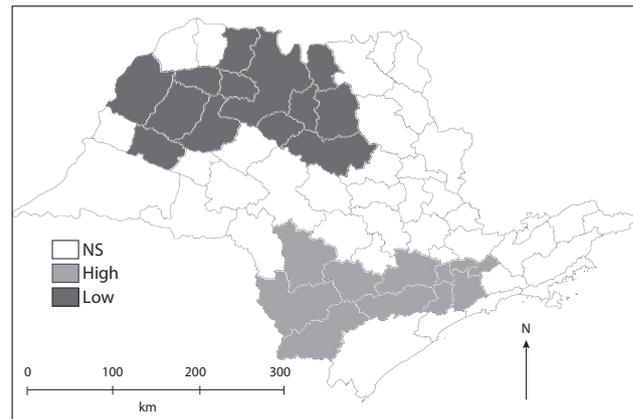
The spatial distribution of the proportion of teenage mothers, by microregion, identified larger proportions in the southern part of the state, in the microregions of Avaré, Itapeva, Capão Bonito, and Registro, close to the border of Paraná, in addition to Ituverava, which is located upstate. Lower rates are located east of the state, in the microregions of Amparo, Campinas, Jundiaí, Osasco, São Paulo, Guarulhos, and São José dos Campos, as well as in Franca and Ribeirão Preto, upstate. Moran's index was  $I = 0.32$  ( $p < 0.01$ ). The distribution of these microregions is similar to that observed for cesarean rates.

The spatial distribution for maternal schooling above eight years of formal education by microregion found higher proportions in the west of the state, bordering the north of the state of Paraná, and in Vale do Paraíba. Moran's index for this variable was  $I = 0.30$  ( $p < 0.01$ ). The spatial distribution of this variable's proportions in the microregions is similar to that of the proportions of cesarean sections.

Regarding the number of medical consultations, the Moran index was positive and significant ( $I = 0.24$ ;  $p < 0.01$ ),

with higher proportions of mothers who had at least 7 consultations in the microregions located in the central, northern and northwestern parts of the state. The lowest proportions are seen in a strip of 12 microregions stretching from east, in the border of the state of Rio de Janeiro, all the way to the state of Paraná, including the Greater São Paulo metropolitan area.

The Moran map for C-section rates is shown in Figure 2 and indicates an area of high priority for intervention in 13 microregions located in the north and northwest of the state, close to the border of the states of Minas Gerais and Mato Grosso do Sul.



**FIGURE 2** Microregions of the state of São Paulo according to priority – high, low and non-significant (NS) – for intervention in rates of cesarean delivery. Microregions in the state of São Paulo, 2003-2007.

cesarean rates were negatively correlated, although not significantly, with the rates of teenage mothers ( $r = -0.14$ ); in contrast, the correlations with educational level ( $r = 0.50$ ) and number of consultations ( $r = 0.60$ ) were statistically significant.

## DISCUSSION

The importance of this study is to identify spatial clusters of microregions with high rates of cesarean delivery. These clusters of micro-regions with high rates of cesarean sections are located in the north and northwest of the state of São Paulo. This is, to our knowledge, the first study using this type of approach.

The data obtained from Datasus refer to all deliveries including those conducted by the Federal Unified Health System (SUS) or private institutions (covered by health plans and pregnant women who receive care in private clinics).

According to the Ministry of Health, C-sections already represent 43% of the deliveries carried out in Brazil both in public and private settings, while the World Health Organization recommends that C-sections are performed in no more than 15% of births, always in situations that involve risks for both mother and child.<sup>11</sup> A study by Barros et al.,<sup>11</sup> conducted in the city of Pelotas (state of Rio Grande do Sul) in 2004 showed an overall cesarean rate of 45%, being 36% performed in patients assisted by the SUS and 81% in the private setting, where 35% of C-sections performed electively. When taking into account private health plans, it appears that this percentage is even higher, reaching 80%.<sup>12</sup>

In the public SUS setting, however, C-sections account for 26% of all births. According to the Interagency Health Information Network (RIPSA, in Portuguese) report in Brazil, from 2008, cesarean deliveries are more common among women with higher levels of education, reaching almost 70% among those with 12 years or more of schooling and being less 20% among women with less formal education. The mother's education variable can be treated as an approximation of maternal social class and remains as the most important factor associated with birth weight and neonatal mortality. A study by Freitas et al.<sup>13</sup> showed that women over age 30 have a higher probability of cesarean delivery than women below 20 years.

Comparing the spatial distribution of cesarean births and mothers under age 20, a higher rate of teenage mothers was observed in areas to the south of the state, where fewer cesarean deliveries are performed, suggesting that microregions with lower socioeconomic development are those with the highest rates of teenage mothers and lower rates of cesarean section. Likewise, Simões et al.<sup>14</sup> analyzed characteristics of adolescent pregnancy in São Luís, Maranhão, and observed that the general characteristics of adolescent mothers differed from older women. In the study presented here, the highest rates of adolescent mothers are concentrated in rural areas with possible compromised infrastructure.

The geographical distribution of the percentages of mothers with more than eight years of education shows a pattern with lower values in the microregions of Registro, Capão Bonito, Piedade, and Paraibuna/Paraitinga, indicating that areas with worst infrastructure are those with higher proportions of mothers with low education and lower rates of cesarean delivery. Similarly, a study by Haidar et al.,<sup>15</sup> conducted in Vale do Paraíba, found that maternal education is strongly associated with type of delivery when mothers with higher levels of education have

a six times greater chance of having their children by cesarean section. This seems to be due to the mother's choice, as much as their physician's. Since cesarean sections are usually more expensive procedures, mothers with higher levels of education and consequently better economic conditions, may opt for it.

This statement must be viewed with caution because some microregions may present lower C-section rates due to areas with worst socioeconomic conditions, where birth care can be precarious to the point of compromising the outcomes of both mother and child.

The spatial patterns for cesarean section according to maternal age and education found in this study were similar to those found by D'Orsi and Carvalho.<sup>16</sup>

After spatial analysis of the distribution of mothers who had at least 7 prenatal consultations, it is clear that the microregions with the highest rates are concentrated in the central, northern and northwestern parts of the state, and these also have higher C-section rates; the Pearson correlation coefficient showed a strong correlation between this variable and cesarean deliveries; the spatial distribution of rates of mothers who had at least seven prenatal consultations reached a significant value for the Moran index. This spatial distribution is similar to that of mothers with high levels of education, suggesting that they initiate prenatal care earlier, possibly, and have more contact with the obstetrician, which facilitates the choice for cesarean delivery.<sup>13</sup> We must remember that a greater number of prenatal consultations can be a sign of a risky pregnancy, which in turn may require cesarean delivery.

As seen in the Moran map, 13 microregions were found as high priority for intervention in order to reduce the rates of cesarean deliveries in northern and northwestern areas of the state, close to the border of Minas Gerais and Mato Grosso do Sul; it is noteworthy that these are microregions with the highest rates of highly educated mothers. Possibly, in regions where coverage of health plans is greater, cesarean rates also tend to be higher.

This study may have limitations, some related to the status of ecological study and other related to the data. The source of the research - Datasus - is widely used in ecological studies but may not have offered socioeconomic information, or information about the type of complications occurred in both vaginal and cesarean deliveries. The impact of cesarean section on the health of the newborn was not mentioned, either; causal relationships cannot be identified, but possible associations can be suggested. Furthermore, neonatal deaths that could be associated with type of delivery were not analyzed.

## CONCLUSION

The identification of these microregion clusters with high rates of cesarean delivery, as well as the identification of microregions with high priority for intervention allows health managers to implement measures in order to minimize these rates.

## RESUMO

Distribuição espacial das cesarianas no Estado de São Paulo.

**Objetivo:** identificar padrões espaciais para partos cesarianos por microrregião do Estado de São Paulo.

**Métodos:** estudo ecológico e exploratório com dados de nascidos vivos entre 2003 e 2007 de 63 microrregiões do Estado de São Paulo. As variáveis analisadas neste estudo foram, além de taxas de parto cesariano, taxas de mães adolescentes, de mães com alta escolaridade e de mães que realizaram pelo menos 7 consultas no pré-natal. Foram calculados os índices de Moran (I), que estimam autocorrelação espacial das taxas das variáveis acima descritas e identificam a presença de aglomerados espaciais. Essas taxas foram visualizadas pelos mapas temáticos; microrregiões com alta prioridade de atenção foram identificadas pelo mapa de Moran. Foram calculados os coeficientes de correlação de Pearson entre as variáveis.

**Resultados:** houve 3.045.293 partos, sendo 1.636.009 (53,72%) partos cesarianos. Foi possível identificar aglomerados espaciais de cesarianas ( $I = 0,58$  e  $p < 0,01$ ) nas microrregiões ao norte e noroeste do Estado, além de Guaraatinguetá. Os valores dos índices de Moran foram, para as taxas de mães adolescentes,  $I = 0,32$ ; para as taxas de alta escolaridade,  $I = 0,30$ ; e para as taxas do número de consultas,  $I = 0,24$ , todos significativos ( $p < 0,01$ ). Foram identificadas microrregiões com alta prioridade de intervenção. As taxas de cesarianas estiveram correlacionadas significativamente com as taxas de alta escolaridade materna e com número de consultas.

**Conclusão:** a identificação desses aglomerados de microrregiões com altas taxas de cesarianas permite aos gestores de saúde implantar políticas para minimizar tais taxas.

**Palavras-chave:** distribuição espacial da população; saúde pública; cesariana; idade materna; escolaridade materna; sistemas de informação geográfica.

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# Identification of hepatitis B virus genotypes in the state of São Paulo

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## SUMMARY

**Objective:** the aim of this study was to identify HBV genotypes in serum samples from patients from the state of São Paulo, received by the viral hepatitis laboratory, at the Virology Centre of Instituto Adolfo Lutz, from various municipalities.

**Methods:** a total of 94 serum samples were randomly analyzed. Genotyping was performed using nested PCR for amplification of S and Pol regions from viral genome. Genotypes were identified comparing the sequences obtained with the sequences deposited in GenBank.

**Results:** we were able to determine the genotype of 91 (97%) samples, as follows: genotype A (55.3%), D (32%), F (5.3%), C (3.2%) and G (1%). There are few data on the epidemiology of genotype G. This genotype has been detected in restricted areas around the world. Frequently, the genotype G infection occurs in HIV-positive male patients. In our case, the sample identified as G was also positive for HIV but in a female patient, which is an uncommon finding in the scientific literature.

**Conclusion:** in this work, we identified the most frequent genotypes in São Paulo as well as the genotype G, rare among the genotypes found in our environment.

**Keywords:** hepatitis B, polymerase chain reaction, genotype, Brazil.

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Conflict of interest: none

## INTRODUCTION

Hepatitis caused by the hepatitis B virus (HBV) is a disease of great importance to public health around the world. Approximately 30% of the world's population, or about 2 billion people, have serologic evidence of current or past infection with HBV. Of these, it is estimated that approximately 360 million people are chronically infected and 600,000 die every year due to acute severe hepatitis, hepatocellular carcinoma or cirrhosis.<sup>1</sup>

HBV has ten distinct genotypes (A to J), identified and defined according to a difference of 8% in their genomic sequences. Recent studies suggest that HBV genotypes may differentially affect the severity of liver diseases such as cirrhosis and hepatocellular carcinoma, as well as response to treatment.<sup>2</sup> The HBV genotypes have distinct geographical distribution. Genotype A is found

mainly in North America and Africa. Genotypes B and C are prevalent in Southeast Asia and the Far East, and the latter has been associated with increased risk of hepatocellular carcinoma. Genotype D has been found throughout the world with the highest prevalence in the Mediterranean, Middle East, South Asia and particularly in India. Genotypes E and F are prevalent in West Africa and Brazil's indigenous population, respectively. Moreover, genotype G has been reported in the USA, France, Colombia and Brazil while genotype H has been found in North and Central America. Recently, through phylogenetic analysis, a new genotype was characterized in Vietnam and Laos, being designated as genotype I,<sup>3,4</sup> while genotype J was identified in Japan.<sup>5</sup> In Brazil, the most common genotype is A, followed by genotypes D and F.

The North, Northeast and Southeast regions have a higher frequency of genotype A, while genotype D is the most common in the South.<sup>6</sup> In some regions, genotypes B and C are also detected at low prevalence, reflecting the presence of descendants of Asian immigrants in these populations.<sup>7</sup> A study conducted in Ribeirão Preto, São Paulo, found genotype D in 56.5% of the cases, genotype A in 41.3%, and genotype in 2.2%.<sup>8</sup> The presence of these genotypes reflects the mix of cultures in Brazil: Native American, European and African backgrounds make the country an important model for studies of population genetics, suggesting an influence of the immigration pattern in each region.<sup>9</sup>

The aim of this study was to identify HBV genotypes in samples received by the viral hepatitis at the Adolfo Lutz Institute, for determining HBV viral load.

## METHODS

### Sampling

During this study, samples from chronic carriers of HBV patients, treated by Public Health Services in the state of São Paulo, were analyzed in order to initiate or monitor treatment. Clinical follow-up and laboratory diagnosis of these patients were performed using commercial tests available throughout Brazil, approved and regulated by the National Health Surveillance Agency (Anvisa) of the Ministry of Health.

The sample consisted of 94 plasma specimens from patients from health centers and public hospitals in the state of São Paulo, in the period comprising June 2010 to May 2011. The samples were stored in a freezer at -20°C and thawed immediately before testing.

### DNA extraction

Extraction of HBV DNA was carried out using the commercial kit QIAamp® DNA Mini and Blood Mini Handbook - QIAGEN®, as described in the manufacturer's instructions.<sup>6</sup>

### Polymerase chain reaction

The polymerase chain reaction (PCR) was performed as described by Kaneko et al.<sup>10,11</sup> with some modifications. The S and Pol regions were amplified according to the protocol reported by Sitnik et al.,<sup>7</sup> for subsequent identification of the HBV genotypes.

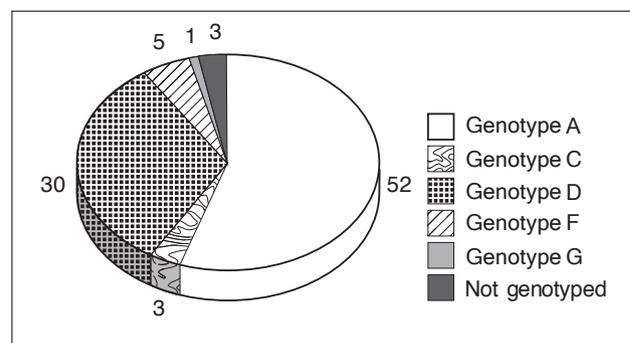
### Sequencing

To determine the genotypes, we used the product amplified by Nested-PCR of S and Pol regions of HBV. The positive samples were sequenced using ABI Prism BigDye™

Terminator V.3.0 kit. The genotypes were confirmed using the genotyping tool available from the NCBI website (<http://www.ncbi.nlm.nih.gov/projects/genotyping/form-page.cgi>).

## RESULTS

Of all the samples analyzed, 50 were from females and 44 from male patients, ages ranged from 1 to 71 years with a median of 40 years. All 94 samples extracted and analyzed by PCR tested positive. Through sequencing, we were able to determine the genotypes of 91 samples (97%) (Figure 1) and genotypes were: A (55.3%), D (32%), F (5.3%), C (3.2%) and G (1%). To confirm the sample identified as genotype G, another extraction, PCR and sequencing were performed.



**FIGURE 1** Distribution of the HBV genotypes identified in samples collected in the state of São Paulo.<sup>2</sup>

## DISCUSSION

HBV genotyping may be an important tool for prognosis of disease progression and treatment. Furthermore, it may be important for understanding the evolution and epidemiology of the virus, since the genotypes vary according to geographic region and often correlated with risk factors.

As expected, the most prevalent genotypes in the study population were genotypes A and D, and these results are consistent with studies on the prevalence of genotypes in Brazil. Genotypes A and D are the most prevalent worldwide, while genotype F is prevalent in the Americas and genotype C is characteristic of the Asian population; genotype C is also quite common in the state of São Paulo. Compri et al.<sup>12</sup> found genotypes A, D and C in children, adolescents and their families in the state of São Paulo. Moraes et al.<sup>13</sup> found genotypes A, D and F in Rio de Janeiro. These same genotypes were also described in populations in Goiânia and Santa Catarina.<sup>14,15,16</sup>

Recent studies have suggested that the rate of lamivudine resistance was higher in patients infected with HBV ge-

notype A than those with genotype D.<sup>17,18</sup> Genotype C has been associated with lower rates of spontaneous clearance of HBeAg in serum compared to infection with genotype B. In addition, genotype C is associated with higher levels of HBV DNA replication, more advanced liver disease, hepatocellular carcinoma, and a decreased rate of response to interferon treatment compared with genotype B.<sup>19</sup>

A strain of genotype G, which is not common in our population, was also identified in this study. The genotype G sample came from a female patient carrying the human immunodeficiency virus (HIV). Bottecchia et al.<sup>20</sup> identified the genotype G in a patient infected with HBV and in only two patients coinfecting with HIV. The presence of genotype G has been associated with sexual relations between men.<sup>21</sup> A study conducted by Sanchez et al.<sup>22</sup> showed a high prevalence of genotype G only in men who have sex with men (MSM) and always coinfecting with another genotype of HBV. In Brazil, Silva et al.<sup>23</sup> identified two patients with genotype G in this population which could somehow be associated with this sexual behavior.

Genotype G was first described in 2000.<sup>24</sup> Later, this genotype was also identified in the United States, Canada, Brazil, Mexico, France, Germany, Vietnam, Thailand, and Japan.<sup>21,25,26</sup> Genotype G is essentially identical to the other HBV genotypes, but has some unique features including an insertion of 36 bp at the gene start codon.<sup>24</sup> Genotype G is the rarest of all HBV genotypes. This genotype is usually found as a coinfection with other HBV genotypes.<sup>26</sup> Work conducted by Bottecchia et al.<sup>20</sup> demonstrated that patients with HBV genotype G presented lamivudine-resistance mutations and large genetic variation among samples, which points out the importance of the circulation of genotype G in Brazil for the treatment of HBV. Nevertheless, epidemiological and clinical data are still limited, probably due to the low incidence worldwide.

Among the approximately 40 million people infected with HIV worldwide, an estimated two million to four million are also chronically infected with HBV.<sup>27</sup> The prevalence rates of HIV/HBV coinfection, obtained in Brazilian studies of samples from health services, are between 5.3% and 24.3%. The increased incidence of chronic complications of viral hepatitis in this population has been observed, which differs from what is seen with other opportunistic diseases. This is explained by increased survival of HIV-infected patients from the use of antiretrovirals. In general, HBV infection tends to be more aggressive in HIV-infected individuals than in mono-infected patients, with highest rates of HBV carriers, higher

HBV viremia levels, more frequent episodes of activation and more rapid progression to cirrhosis.<sup>27</sup>

The identification and determination of epidemiology and molecular characteristics of circulating HBV genotypes is important and can be a tool for prognosis and treatment of HBV as well as the hepatitis C virus (HCV). Furthermore, it demonstrates the circulation of different viral strains in Brazil. Clinical follow-up of individuals with chronic HBV infection should be one of the concerns, making it necessary to implement continuous measures of prevention-based health education. The most effective measure to combat HBV infection is active immunization of susceptible individuals, using currently available vaccines, which are highly efficient and safe, in addition to encouraging the use of condoms, and spreading information on the risk presented by manicures and drug users. These measures enable the creation of programs for infection control, seeking eventual eradication of hepatitis B and prophylaxis of hepatocellular carcinoma.<sup>28</sup>

## CONCLUSION

In this study, we identify the HBV genotypes prevalent in the state of São Paulo. Genotypes identified are those already described in previous studies, and we also found a sample infected with genotype G, a rare genotype, associated with men who have sex with other men, HIV-positive. However, in our study, genotype G was found in a female HIV-infected patient, which demonstrates the relevance and need of genotyping a larger number of patients. Genotyping is an important tool for prognosis of disease progression, treatment, and better understanding of the virus' evolution and epidemiology, since genotypes vary according to geographical regions and often correlate with risk factors.

Project approved on 9/29/2009 by the Research Ethics Committee of the Adolfo Lutz Institute – CEPIAL (CCD-BM 06/2009), according to Resolution 196/96 on research involving human subjects, published by the National Health Council – Ministry of Health – Brasília (1996).

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## RESUMO

Identificação dos genótipos do vírus da hepatite B no Estado de São Paulo.

**Objetivo:** o objetivo deste estudo foi identificar os genótipos do HBV nas amostras de soros recebidas pelo Laboratório de Hepatites do Centro de Virologia do Instituto Adolfo Lutz.

**Métodos:** foram analisadas aleatoriamente 94 amostras de soropositivas, provenientes de diversos municípios do Estado de São Paulo. Para determinação dos genótipos, foi realizada Nested-PCR das regiões S e Pol do HBV. Os genótipos foram identificados comparando os resultados amplificados com as sequências depositadas no GenBank. **Resultados:** foi possível determinar o genótipo de 91 (97%) amostras do total analisado e os genótipos identificados foram: genótipos A (55,3%), D (32%), F (5,3%), C (3,2%) e G (1%). Há poucos dados a respeito da epidemiologia do genótipo G. Esse genótipo tem sido detectado em áreas restritas do mundo. Geralmente, a infecção pelo genótipo G ocorre em indivíduos HIV positivos do sexo masculino. Neste trabalho, a amostra identificada como G foi também positiva para HIV e era de uma paciente do sexo feminino, dado raro na literatura científica.

**Conclusão:** neste trabalho, foram identificados os genótipos mais frequentes, assim como uma cepa do genótipo G, rara entre os encontrados em nosso meio.

**Palavras-chave:** hepatite B; reação em cadeia da polimerase; genótipo; Brasil.

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# Reeducation of pelvic floor muscles in volleyball athletes

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## SUMMARY

**Objective:** to verify the effectiveness of the pelvic floor muscles rehabilitation program (PFMRP) in female volleyball athletes, analyzing the amount and frequency of urinary leakage.

**Methods:** experimental study. The sample consisted of 32 female athletes from Famalicão Athletic Volleyball Club (Portugal). The athletes were selected by convenience and distributed randomly into two groups: experimental group (EG = 16 athletes) and the control group (CG = 16 athletes). The EG underwent PFMRP for three months. The PFMRP was the awareness and identification of the pelvic floor muscles (PFM), pre-timed PFM contraction prior to occasions of increased intra-abdominal pressure, and 30 daily contractions of MPP at home. The CG had only access to the pamphlet. The assessment instruments included the questionnaires, the Pad Test (amount of urinary leakage) and frequency record of urinary leakage (7-day diary) before and after PFMRP.

**Results:** the amount of urine leakage decreased in 45.5% of athletes under PFMRP intervention, and in 4.9% of athletes in CG, with statistical differences between the groups ( $p < 0.001$ ). The reduction in the frequency of urinary leakage was 14.3% in EG, and 0.05% in CG, a statistically significant difference between the groups ( $p < 0.001$ ).

**Conclusion:** PFMRP in this study was effective to reduce stress urinary incontinence in female volleyball athletes. The program allowed significant improvement of symptoms of quantity and frequency of urinary leakage.

**Keywords:** sports athletes, stress urinary incontinence, physical therapy.

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## INTRODUCTION

There is a general consensus among authors that despite the distinct benefits of sport in young athletes, such as improved cardiovascular and respiratory systems, the reduction of adipocytes, increased endurance, muscular hypertrophy and increased strength, and higher bone density, adversely urogynecologic problems arising from physical activity may occur, including amenorrhea, oligomenorrhea, short phase of the *corpus luteum*, anovulation and urinary incontinence.<sup>1</sup>

In the last decade, several studies have demonstrated and reflected the association between urinary incontinence (UI) and high-impact sports.<sup>1,2</sup>

Epidemiological studies related pregnancy and childbirth as probable primary etiologic factors of stress uri-

nary incontinence (SUI). In fact, the prevalence of SUI is higher in multiparous women than in nulliparous.<sup>3</sup> However, a recent study of SUI in young nulliparous athletes showed a prevalence of 36.4%.<sup>4</sup>

Some studies have shown that the high prevalence of SUI in nulliparous athletes is associated with the type of sport. A systematic review conducted in 2004,<sup>2</sup> revealed that the prevalence of UI during sports practice varied between 0% (golf) and 80% (trampoline).

Modalities that include activities such as jumping and running seem to have an increased risk of triggering urinary leakage in athletes, due to sudden increase in intra-abdominal pressure.<sup>5</sup> Hay<sup>6</sup> noted that the impact on the pelvic floor while running is three to four times the body

weight, five to twelve times while jumping, nine times in the case of pole vault, and more than nine times in the practice of high jump. The sudden increase in intra-abdominal pressure associated with sports and abdominal and pelvic muscle imbalance is the main risk factor for SUI in young nulliparous athletes.<sup>7</sup> Some theories based on risk factors have been developed to explain the occurrence of UI in young nulliparous athletes. The muscle dysfunction in pelvic floor associated with the stretching of the pubo-cervical fascia results in hypermobility of the bladder neck. This dysfunction is triggered by the action of jumping, which causes direct injury to the structures of the pelvic floor. The fatigue of the Pelvic Floor Muscles (PFM) caused by high repetition of running and jumping activities results in decreased blood flow to the muscle fibers with depletion of nutrients and oxygen.<sup>2,8</sup>

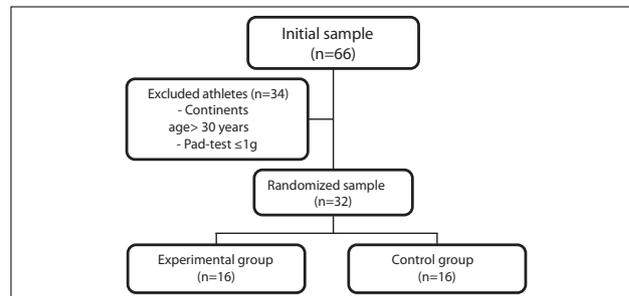
The pelvic floor muscles rehabilitation programs (PFMRP) are currently the first-line intervention in the treatment of SUI in women with incontinence and associated risk factors.<sup>9</sup> These PFMRP include different treatment approaches such as biofeedback, electrical stimulation, manual strengthening techniques, vaginal cones and exercises to strengthen the pelvic floor muscles (PFM).<sup>9,10</sup> PFMRPs that only include teaching proper PFM contraction, awareness of pelvic floor in the body function, and functional interaction between PFM and the muscles forming the abdominal wall have shown cure rates from 56 to 70% in women with urinary incontinence and associated risk factors.<sup>10</sup> Investigations showed a reduction in the frequency and amount of UI episodes and increased strength of PFM in 6 to 12 weeks.<sup>10-12</sup>

The relevance of this study lies in the lack of randomized controlled studies in athletes, the lack of awareness among health professionals, coaches and athletes for the prevention and treatment of UI. Therefore, the aim of this investigation was to verify the effectiveness of a program of rehabilitation of the pelvic floor muscles (PFMRP) in federated nulliparous athletes.

## METHODS

The study is experimental in nature, and the initial sample consisted of sixty-six female athletes from Famalicão Athletic Volleyball Club (Figure 1). The final sample consisted of thirty-two athletes with symptoms of stress urinary incontinence, randomly divided in two groups: experimental group and control group, both with sixteen athletes (Figure 1). A lottery design was used for randomization of the sample, i.e., 32 folded pieces of paper were placed in a common box, so that 16 were assigned the number 1 (control group) and the remaining were marked as number 2 (experimental group). Each athlete wi-

threw from the box a single piece of paper, without knowledge of the meaning of that number, which ensured blinding of participants.



**FIGURE 1** Sample selection.

Sample selection began in the last week of December 2011, using a baseline questionnaire and pad-test. Inclusion criteria included nulliparous female volleyball athletes, symptoms of stress UI, age between 13 and 30 years, and amount of urinary leakage greater than 1 g. Exclusion criteria were treatment for less than six months, sport practice for less than two years, repeated urinary infections or at the time of sample selection, body mass index below 18 kg/m<sup>2</sup> or above 25 kg/m<sup>2</sup>, and PFMRP adherence under 50%.

The study was previously approved by the president of the club, and informed consent given by either the athletes or their legal guardians.

In the last week of December 2011, both groups underwent a baseline questionnaire, pad test and assessment of frequency of urinary leakage (urinary diary). Three months after introduction of PFMRP, in the first week of May 2012, the groups were once again assessed through a final questionnaire (attached), pad test and frequency of urinary leakage. The frequency of UI episodes consisted of a daily log of urinary leakage for seven consecutive days.<sup>13</sup> The amount of urinary leakage was assessed by pad test, in the first 15 minutes of volleyball practice.<sup>14</sup> A preweighed sanitary pad branded Carefree Essentials™ was properly placed before training. After 15 minutes of physical activity, the pad was removed and weighed on a Kenwood Ds700 digital scale. Athletes were considered incontinent with losses exceeding one gram.<sup>15</sup>

EG underwent PFMRP, which initially consisted of educational action, awareness of PFM and receipt of the information pamphlet. CG only had access to the pamphlet, which displayed a summary of the educational action.

The educational action included teaching of the anatomy and physiology of the lower urinary tract, concepts of UI and SUI, etiology of SUI in athletes, preventive strategies for urinary leakage, exercise-related disorders in athletes, location of the PF muscles, identification and

awareness of correct contraction of PFM, types of PFM contraction, *Knack* technique and knowledge of PFM exercises to be performed at home.

The educational action also included a urinary diary for EG. The urinary diary consisted of daily records of the amount of liquid intake, urinary frequency and volume for three consecutive days. The urinary diary enabled an improved perception of the changes in everyday life behavior and hygiene. The PFM exercises that the athletes would be required to perform at home included 30 sustained contractions and four quick contractions after each sustained contraction, in different positions and daily for three months.

Weekly visits were made at the club during the study period to ensure motivation and adherence to PFM RP in EG both at home and after the training sessions.

Normality of variables was assessed in the statistical analysis with the nonparametric test of Shapiro-Wilk, and the Student t-test was applied for independent and paired samples. At the intersection of variables, the Chi-square test was used. Whenever the applicability conditions were not met, we used the Fisher's alternative exact test. All data were collected and analyzed using SPSS, version 20.0, with a significance level of 5%.

## RESULTS

The characterization of the sample groups revealed no statistically significant differences in all parameters. The groups are homogeneous and can be compared (Table 1).

**TABLE 1** Sample characterization of the experimental group (EG) and control group (CG)

	EG (n = 16)	CG (n = 16)	p <sup>+</sup>
	$\bar{x} \pm SD$ (min-max)	$\bar{x} \pm SD$ (min-max)	
<b>Demographics</b>			
Age (years)	19.4 ± 3.24 (16-25)	19.1 ± 2.11 (17-26)	0.749
BMI (kg/m <sup>2</sup> )	22.8 ± 2.57 (19.2-24.9)	21.5 ± 1.81 (19.2-24.1)	0.135
Duration of UI (years)	2.4 ± 1.67 (1-4)	1.6 ± 0.72 (1-6)	0.064
<b>Characteristics of the sport</b>			
Sports practice (years)	6.9 ± 4.09 (2-12)	4.9 ± 2.51 (3-15)	0.106
Weekly training sessions (number)	3.6 ± 0.93 (3-6)	4.8 ± 0.61 (3-6)	0.745
<b>Characterization of SUI</b>			
Frequency of leakage	<b>n (%)</b>	<b>n (%)</b>	0.113 <sup>#</sup>
Once or several times in a month	5 (31.3%)	8 (50%)	
Once or several times in a week	11 (68.8%)	8 (50%)	
<b>Amount of urinary leakage</b>			
Drops	7 (43.8%)	6 (37.5%)	0.685 <sup>#</sup>
Small amount (weak stream of urine)	9 (56.3)	10 (62.5%)	
<b>Severity of UI</b>			
Low	1 (6.2%)	5 (31.2%)	0.109 <sup>#</sup>
Moderate	10 (62.5%)	5 (31.2%)	
High	5 (31.2%)	6 (37.5%)	
<b>Triggering activities</b>			
Training	14 (87.5%)	13 (81.3%)	1.000 <sup>*</sup>
Competition	2 (12.5%)	3 (18.8%)	
<b>Activities of daily life</b>			
Yes	3 (37.5%)	6 (37.5%)	0.433 <sup>*</sup>
No	13 (62.5%)	10 (62.5%)	
<b>Prevention strategies for urinary leakage sanitary pads (during sports)</b>			
Yes	11 (68.8%)	11 (68.8%)	1.000 <sup>#</sup>
No	5 (31.2%)	5 (31.2%)	
<b>Bathroom (prior to sports)</b>			
Yes	14 (87.5%)	16 (100%)	0.484 <sup>*</sup>
No	2 (12.5%)	0 (0.00%)	
<b>Reducing the amount of liquid intake (prior to sports)</b>			
Yes	9 (56.3%)	8 (50.0%)	0.723 <sup>#</sup>
No	7 (43.8%)	8 (50.0%)	

$\bar{x} \pm SD$  = mean and standard deviation.

<sup>T</sup>-Student test for two independent samples.

<sup>#</sup>Chi-squared test.

<sup>\*</sup>Fisher's exact test.

The variation of the initial and final mean values showed a statistically significant decrease in the amount of urinary leakage in EG, while in CG no significant differences were seen at the end of the study. In EG, the mean value fell 45.5% while in CG, the decrease reached 4.9%, which represents a significant difference between the groups (Table 2).

**TABLE 2** Intra- and inter-group comparison of the variation in amount of urinary leakage

	EG (n = 16)	P	CG (n = 16)	P
	$\bar{X} \pm SD$ (min-max)		$\bar{X} \pm SD$ (min-max)	
Pad-test variation (Final-initial)	(-) 2 ± 1.28 (1-4.5)	<0.001*	(-) 0.2 ± 0.41 (0.3-1.2)	0.324 <0.001+

$\bar{X} \pm SD$ = mean and standard deviation.  
\*p<0.05 intra-group.  
+p<0.05 inter-group.

The variation between the initial and final mean value for frequency of UI episodes was statistically significant in EG (Table 3).

In terms of variation of mean values, there was significant reduction in the frequency of UI episodes in 14.3% of the subjects in EG, and in 0.05% of the women in CG. This decrease in variation in UI episodes was significant between the groups (Table 3).

**TABLE 3** Intra- and inter-group comparison of the variation in the frequency of incontinence episodes

	EG (n=16)	P	CG (n=16)	P
	$\bar{X} \pm SD$ (min-max)		$\bar{X} \pm SD$ (min-max)	
Variation of FIE (Final-initial)	(-) 0.3 ± 0.50 (0-2)	<0.001*	(-) 0.1 ± 0.44 (0-3)	0.414 <0.001+

$\bar{X} \pm SD$ =mean and standard deviation; FIE=frequency of incontinence episodes.  
\*p<0.05 intra-group.  
+p<0.05 inter-group.

## DISCUSSION

The importance of sports for women’s general health, the increasing need for knowledge about the effects of high impact sports activities on lower urinary tract and the evidence of treatment of UI in nulliparous athletes have recently fueled scientific research in this area.<sup>2,16</sup>

In the present study, the characterization of the total sample revealed a mean age of 19 years. According to

a study by BØ & Borgen,<sup>8</sup> the prevalence of urinary leakage in female athletes occurs between 15 and 39 years old.

In the analysis of BMI, the athletes’ total mean was 22 Kg/m<sup>2</sup>, considered by the National Health Nutrition Examination Survey as normal weight. In the study by BØ & Borgen,<sup>8</sup> the mean BMI of the athletes was also one of normal body weight, which is consistent with the results obtained in the present study. Waldrop<sup>17</sup> reported that metabolic and hormonal changes in athletes can result in UI. Hormonal deficits (hypoestrogenism) reduce blood flow in arteriovenous plexus, mucosal coaptation, and urethral pressure, promoting IU.<sup>17,18</sup>

In this study, the parameters of frequency and amount of urinary leakage were used to determine the degree of UI, showing a greater percentage of athletes with moderate severity. Roza et al.<sup>20</sup> found mild and moderate UI in sports such as track and field, basketball, volleyball and handball. The severity of UI increases with the type and the continuity of high-impact sports (running, jumping), with equally progressive consequences both for sports performance and the quality of life of female athletes. In the present study, none of the athletes resorted to a doctor for early intervention and to prevent worsening of the condition. Thyssen et al.,<sup>16</sup> in a sample of young dance athletes, showed that only 3.3% told a doctor about the symptoms of urinary incontinence.

In this study, the highest percentage of urinary leakage was triggered during training, 87.5% in EG and 81.3% in CG. These results are in agreement with the study by Thyssen et al.,<sup>16</sup> who demonstrated that athletes who practice sports such as gymnastics, basketball, volleyball and handball had 95.2% of urinary leakage during training against 51.2% during competitions. This aspect can be explained by the high level of catecholamines in stress situations, such as in competitions.<sup>16</sup>

The present study demonstrated that athletes of both groups resorted to strategies or measures to prevent urinary leakage. In decreasing order, the measure most commonly used to conceal urinary leakage was the use of a sanitary pad, followed by bladder emptying and the reduction of fluid intake before training. Eliasson et al.<sup>20</sup> found the same strategies in a sample of 18 gymnastics athletes.

In this study’s baseline assessment, the groups showed no significant differences regarding the amount of urinary leakage (pad-test). After three months of PFM RP, EG reduced significantly the occurrence of urinary leakage, down 45.5% compared with 4.9% in CG, statistically significant differences being found between the groups.

The baseline mean value found for amount of urinary leakage in this study was 4.4 g. In a study published by Eliasson et al.,<sup>20</sup> which included a sample of 18 gymnastics athletes, the average amount of urinary leakage was 28 g (9-56 g). This difference can be explained by the type of sport, since gymnastics presents more impact than volleyball.<sup>2,16</sup>

Regarding the frequency of urinary leakage, baseline assessment showed an average frequency of 2.1 episodes in seven days, falling to 1.8 (14.3%) episodes in EG and 1.9 (0.05%) in CG by the end of the study period. By the end of the study, GE significantly decreased the frequency of urinary leakage compared to CG ( $p < 0,001$ ).

A single study was published, including a small sample of volleyball players, with a combined treatment program (biofeedback, electrical stimulation, PFM strengthening exercises and vaginal cones). And after 4 months of intervention, the results showed that the program was effective in reducing the use of sanitary pads and symptoms of urinary leakage during volleyball training and activities of daily life.<sup>21</sup>

## CONCLUSION

This study leads to the conclusion that the program of rehabilitation of pelvic floor muscles in this sample was effective for the reduction of stress urinary incontinence in volleyball athletes. The program of rehabilitation of the pelvic floor muscles allowed a significant improvement of clinical symptoms in the amount and frequency of urinary leakage.

## RESUMO

Reeducação dos músculos do pavimento pélvico em atletas de voleibol.

**Objetivo:** verificar a eficácia do programa de reeducação dos músculos do pavimento pélvico (PRMPP) em atletas femininas de voleibol, analisando a quantidade e a frequência das perdas urinárias.

**Métodos:** estudo experimental. A amostra foi constituída por 32 atletas do sexo feminino do Atlético Voleibol Clube de Famalicão (Portugal). As atletas foram selecionadas por conveniência e distribuídas aleatoriamente em dois grupos: o grupo experimental (GE = 16 atletas) e o grupo-controle (GC = 16 atletas). O GE foi submetido ao PRMPP durante 3 meses; o programa consistiu na conscientização e identificação dos músculos do pavimento pélvico (MPP), na pré-contração dos MPP ao aumento da pressão intra-abdominal, e em 30 contrações diárias dos

MPP no domicílio. O GC teve acesso unicamente ao banheiro. Os instrumentos de avaliação englobaram os questionários, o *pad-test* (quantidade de perda urinária) e o registro da frequência das perdas urinárias (diário de 7 dias), antes e após o PRMPP.

**Resultados:** a quantidade de perda urinária diminuiu 45,5% no GE, com intervenção do PRMPP, e 4,9% nas atletas do GC, verificando-se diferenças estatisticamente significativas entre os grupos ( $p < 0,001$ ). Na frequência das perdas urinárias, a redução foi de 14,3% no GE e de 0,05% no GC, verificando-se diferenças estatisticamente significativas entre os grupos ( $p < 0,001$ ).

**Conclusão:** o PRMPP, nessa amostra, foi eficaz na incontinência urinária de esforço em atletas do sexo feminino de voleibol, pois permitiu melhorar significativamente os sintomas de quantidade e frequência das perdas urinárias.

**Palavras-chave:** atletas desportivas, incontinência urinária de esforço, fisioterapia.

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# Expansion of morbidity: trends in healthy life expectancy of the elderly population

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## SUMMARY

**Objective:** to analyze the changes in life expectancy (LE) and disability-free life expectancy (DFLE) in São Paulo's elderly population to assess the occurrence of compression or expansion of morbidity, between 2000 and 2010.

**Methods:** cross-sectional and population survey, based on official data for the city of São Paulo, Brazil, and data obtained from the Health, Well-Being and Aging Survey (SABE). Functional disability was defined as difficulty in performing at least one basic activity of daily living. The Sullivan method was used to calculate LE and DFLE for the years 2000 to 2010.

**Results:** from 2000 to 2010, there was an increase in disabled life expectancy (DLE) in all age groups and both sexes. The proportion of years of life free of disability, at 60 years of age, decreased from 57.94% to 46.23% in women, and from 75.34% to 63.65% in men. At 75 years of age, this ratio decreased from 47.55% to 34.54% in women, and from 61.31% to 56.01% in men.

**Conclusion:** the expansion of morbidity is an ongoing process in the elderly population of the municipality of São Paulo, in the period of 2000-2010. These results can contribute to the development of preventive strategies and planning of adequate health services to future generations of seniors.

**Keywords:** life expectancy, active life expectancy, life tables, morbidity, elderly.

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## INTRODUCTION

Brazil is a country that has had one of the fastest population aging processes in recent times. The proportion of elderly (aged  $\geq 60$  years) increased from 4.6% in 1950 to 8.7% in 2010.<sup>1</sup> In 2050, Brazil will be one of six countries with the highest proportion of elderly individuals (approximately 60 million).<sup>1</sup>

As aging is associated with increased prevalence of chronic diseases, it is essential to investigate under what conditions the years gained with increased life expectancy of the Brazilian population will be lived, in order to contribute to the knowledge of the needs of the elderly and provide data for the allocation of health resources and planning of public policies.<sup>2</sup>

Therefore, three hypotheses were formulated in order to discuss the effect of changing patterns of morbidity and mortality in the health status of the populations.<sup>3,4</sup>

The first hypothesis is known as the compression of morbidity, and suggests that life expectancy has reached adult biological limits. As a result, if the incidence of di-

sabling diseases can be extended, morbidity will then be compressed to a shorter period of time.<sup>5,6</sup>

The second hypothesis proposes that the decline in mortality derives from a reduction in the case fatality rates of diseases and not from reductions in their incidence or progression. Thus, the decline in mortality is accompanied by an increase in the number of people with chronic disease and disability.<sup>7</sup>

The third hypothesis states that the decline in mortality is partly due to the decline in disease lethality, but at the same time the incidence and progression of chronic diseases should fall, leading to a dynamic equilibrium. According to this idea, the years with severe morbidity and disability remain relatively constant, since medical interventions and changes in lifestyle reduce the rate of progression of chronic diseases.<sup>8</sup>

The concept of healthy life expectancy, proposed in the 1960s<sup>9</sup> and developed in the 1970s,<sup>10</sup> refers to the average number of years of life that people of a certain age

can expect to live healthy<sup>11</sup> and can be used to assess the occurrence of compression of morbidity in a population.<sup>12</sup> Indicators of healthy life expectancy, such as disability-free life expectancy (DFLE), can provide information not only on the prevalence of functional disability, but also on the potential duration of disability and the time during which a given population will need health care.<sup>13</sup>

In Brazil, a few studies have evaluated the healthy life expectancy of the general population and the elderly population. In 2005, Romero and colleagues evaluated the healthy life expectancy of the population, based on information obtained from the database of the Brazilian Census Bureau (IBGE), using two approaches: one from the self-assessment of health status and the other based on the self-assessment of limitations in activities of daily living. The authors showed that both approaches showed very similar estimates, particularly in populations with older age and the proportion of lost years of healthy life is more important in women.<sup>14</sup>

Also in 2005, Camargo and colleagues used a database of 2000 belonging to the Health, Well-Being and Aging (SABE) survey and, by assessing the life expectancy with functional disability in elderly individuals in São Paulo, they showed that, although older women in this city presented higher life expectancy compared to men, the proportion of years lived free of disability was lower.<sup>15</sup>

In 2009, Camargos and colleagues, using the self-perception of health status, categorized into good or bad, as a measure of health status in older individuals using information obtained from the National Survey by Household Sampling (PNAD) of 2003, estimated a healthy life expectancy for the Brazilian population aged 60 years and older. The estimates also revealed that women live longer, but the number of years they live with a perception of poor health is greater than the estimate for older men.<sup>16</sup>

In 2011, another study based on the SABE survey and which used longitudinal data reinforced the stronger impact of disability in females, evidenced by the higher life expectancy of women with disabilities.<sup>17</sup>

Given that in the Brazilian context the time trends of healthy life expectancy in the elderly population haven't been evaluated yet, indicators such as disability-free life expectancy (DFLE) may provide key information for the planning of health care in this population.

The aim of this study is to analyze the changes in life expectancy and disability-free life expectancy in elderly individuals living in São Paulo, from 2000 to 2010, based on the SABE survey, in order to evaluate the occurrence of compression or expansion morbidity in this population.

## METHODS

### Study design and sampling

Repeated cross-sectional study using data from SABE survey - Health, Well-Being and Aging, which constitutes a population-based survey aimed to assess the living conditions of the elderly in seven cities of Latin America and the Caribbean (Argentina, Barbados, Brazil, Chile, Cuba, Mexico and Uruguay).<sup>18</sup>

In Brazil, the SABE survey was initiated in 2000 in São Paulo's metropolitan area, including 2143 elderly individuals aged 60 years or older of both genders. The sampling was random and representative of the elderly population in São Paulo in 1996, which totaled 836,223.<sup>19</sup> The sample was initially composed of 1568 individuals, being extended to 2143 in order to increase the number of male seniors aged 75 years or older, due to the higher mortality rate in this age group and gender.<sup>20</sup> To obtain the desired number of elderly individuals, we defined the minimum number of 5882 households to be randomly selected according to the expression  $[d=(1500*10/3)/0.85]$ , where  $d$  is the lowest number of households being selected; 1500, the lowest number of elderly individuals to enable the desired analyses; the 10/3 ration being 3 elderly for every 10 households; and 0.85, the expected rate of success for locating and interviewing in the selected households.<sup>20</sup>

For the random selection of households, we used a two-staged cluster sampling, selected by a criterion of distribution proportional to size:

- First stage - for sampling this stage, the permanent records of 72 *census* segments in the National Survey by Household Sampling (PNAD) of 1995 were used, calculated as  $f_1=(72*D_i)/D$ , where  $f_1$  is the sampling fraction of this stage,  $D_i$  is the number of households in each segment; and  $D$  is the total number of households in the city of São Paulo.
- Second stage - to sample this stage, the number of households to be randomly selected was calculated, according to the number of *census* segments ( $5882/72=81.69$ , approximate value used is 90), defined by  $f_2=90/D_i$ , based on the use of addresses, according to the PNAD of 1998.

The probability of a household belonging to the selected sample was defined as  $f=f_1*f_2$ . In the selected households, 1852 eligible elderly were identified, of whom 1568 agreed to participate in the study (84.67%).

The samples were supplemented with subjects aged  $\geq 75$  years and males including households located near

the selected areas or, at most, within the boundaries of the districts of the selected areas.

To adjust the distribution of the sample to the composition of the population, weights were calculated for each sex and age group. To compensate for unequal probabilities of random selection in the second stage due to updating address lists for the 1998 PNAD, weights were calculated for each *census* segment.

A detailed description of the methods employed in the SABE survey can be found in the book *O Projeto SABE no Município de São Paulo: uma abordagem inicial* [available from <http://www.fsp.usp.br/sabe>].

In 2010, a new sample for the SABE survey was performed including 907 individuals of both genders, aged  $\geq 60$  years. The details of the methods employed are described in other publications.<sup>17, 18</sup>

#### Data collection

Data were collected through a questionnaire prepared by a regional committee, composed of leading researchers from each participating country and experts in specific research topics. The instrument consists of eleven sections covering aspects of daily life of the elderly: personal data, cognitive assessment, health status, functional status, medications, use of and access to services, network of family and social support, employment history and income sources, housing characteristics, anthropometry, flexibility and mobility.

The interviews were conducted at home, in the years 2000 and 2001 (the 2000 cohort) and in the years 2010, 2011 and 2012 (the 2010 cohort). Where there was difficulty or impossibility of the elderly to respond (due to physical or cognitive problems), the participation of someone close was requested.<sup>17, 21</sup>

#### Selected variables

Among the sociodemographic variables, the following were considered: age, gender, living arrangements, marital status, ethnicity, education and income, based on relevant scientific literature.<sup>22, 23</sup>

Age was measured continuously, and categorized as 60-64 years, 65-69 years, 70-74 years, 75-79 years and 80 years and older. The family arrangement was classified as living alone or not living alone. With regard to education, information was collected and categorized as: no formal education, primary school, high school, or undergraduate/graduate education. Marital status was categorized into: single, married/common-law partner, widowed, or divorced/separated. The employment status was classified as currently employed or unemployed.

Functional disability was defined as difficulty in performing one or more activities of daily living, including:

getting dressed, eating, bathing, toileting, walking around, fecal and/or urinary incontinence, based on a validated questionnaire already used in other publications.<sup>15, 17, 24</sup>

#### Statistical Analysis and Ethical Aspects

Abridged life tables for the interval beginning with 60 years of age were calculated for the years 2000 and 2010 based on mortality and morbidity information<sup>10</sup> and following steps described in demographics manuals,<sup>25</sup> according to the Sullivan method.<sup>10</sup>

The information required for the application of the Sullivan method is: specific mortality rates for a given population to allow the construction of a life table and the prevalence of health states (disability) according to age.<sup>14</sup>

To calculate the disability-free life expectancy (DFLE), the following applied:

$$EVLI_x = \frac{\sum_{i=x}^w YWD_i}{l_x}$$

The acronyms used were in accordance with the international notation, meaning:

$l_x$  = number of survivors at age  $x$  in the hypothetical cohort of the table;  $YWD$  = number of years lived without disability;  $DFLE_x$  = sum of years lived without disability for ages  $x$  and over, divided by  $l_x$ .

The elderly population estimated for mid-year 2000 and mid-2010 was obtained from the *censuses* of 2000 and 2010, as well as information on deaths in the elderly population, gathered from Fundação Sistema Estadual de Análise de Dados.<sup>26</sup>

In analyzes involving inference from the sample, the information from each individual were weighted by the inverse of the sampling fraction, with corrections for stratification and non-response.

The weights resulting from the sample design, i.e. the inverse of the sampling fractions, were adjusted in order to represent the population of the municipality by post-stratification. The weight of each individual indicates how many inhabitants in the city it represents, and thus the estimates of means and proportions are weighted to represent population estimates.

Relative frequencies (%) were used to analyze the prevalence and the Rao-Scott test for associations. Analyses were performed using Microsoft Excel 2007 software (calculation of the life tables) and Stata, version 11.1 (descriptive analyzes of socio-demographic variables and functional disability). In the latter case, the weight of the sample (svy command) was taken into account.

The research project was submitted to the respective ethics committees of the countries involved. In Brazil, the project was approved by the Ethics Committee on Human Research of the Faculty of Public Health, University of São Paulo (COEP Notice 67/99 and COEP Notice 83/06 – Research Protocol n° 1345).

#### Data interpretation

Changes in expectations of healthy life were classified into four possible situations:<sup>12</sup>

1. Absolute compression and relative compression of morbidity: there is a decrease in disabled life expectancy (DLE) and an increase in percentage of disability-free life expectancy (DFLE) in the overall life expectancy (LE).
2. Absolute compression and relative expansion of morbidity: there is a decrease in disabled life expectancy (DLE) and a decrease in percentage of disability-free life expectancy (DFLE) in the overall life expectancy (LE).
3. Absolute expansion and relative compression of morbidity: there is an increase in disabled life expectancy (DLE) and an increase in percentage of disability-free life expectancy (DFLE) in the overall life expectancy (LE).

4. Absolute expansion and relative expansion of morbidity: there is an increase in disabled life expectancy (DLE) and a decrease in percentage of disability-free life expectancy (DFLE) in the overall life expectancy (LE).

## RESULTS

In 2000, we evaluated 2,143 elderly (response rate 84.6%), 58.6% being female. In 2010, 907 individuals (response rate 91.6%) were assessed, 64.6% being female.

According to Table 1, in 2000, the percentage of women in the age group of 75 years or more was higher than that of men. In 2010, however, the difference in the distribution of the elderly by gender was not significant. Regarding ethnicity, there was a higher percentage of whites, both among men and women. In terms of education, a higher percentage of men had graduated from high school and college, in 2000 and 2010. Widowhood was more prevalent among women than men, also with a higher percentage of single women. We found a higher percentage of men working at the time of the study and women who lived alone, both in 2000 and 2010 (Table 1).

**TABLE 1** Distribution of the elderly by sex according to socio-demographic variables. SABE<sup>1</sup> Survey, São Paulo, Brazil, 2000 - 2010

Variable	2000 (%) Female/Male	p	2010 (%) Female/Male	p
<b>Age range (years)</b>				
60-74	75.8 / 80.8		56.5 / 63.0	
≥ 75 years	24.2 / 19.2		43.5 / 37.0	
Total	100.0	0.0030	100.0	0.0894
<b>Ethnicity</b>				
White	76.7 / 76.6		62.8 / 62.2	
Mixed	14.0 / 14.2		25.7 / 22.7	
Black	4.4 / 4.1		6.4 / 8.8	
Yellow/other	4.9 / 5.1		5.1 / 6.2	
Total	100.0	0.9535	100.0	0.4329
<b>Education</b>				
No formal education	23.4 / 18.3		17.3 / 12.6	
Primary school	66.1 / 64.5		70.9 / 66.5	
High school	6.8 / 8.9		6.9 / 11.5	
Undergraduate/graduate	3.7 / 8.3		5.0 / 9.4	
Total	100.0	<0.000	100.0	0.0036
<b>Marital status</b>				
Single	5.3 / 4.4		4.9 / 3.5	
Married	37.5 / 70.4		35.4 / 76.8	
Widowed	43.2 / 14.5		51.4 / 15.6	
Divorced/separated	14.0 / 10.7		8.2 / 4.1	
Total	100.0	<0.000	100.0	<0.000
<b>Employment status</b>				
Currently employed	19.1 / 40.5		12.7 / 39.9	
Currently unemployed	80.9 / 59.5		87.3 / 60.1	
Total	100.0	<0.000	100.0	<0.000
<b>Household arrangement</b>				
Living alone	17.1 / 7.7		21.4 / 8.3	
Not living alone	82.9 / 92.3		78.6 / 91.7	
Total	100.0	<0.000	100.0	<0.000

<sup>1</sup>available from: <http://www.fsp.usp.br/sabe>.

Table 2 shows the prevalence of disability according to age group. In general, there is a higher prevalence of disability with increasing age. The percentages of disability were higher in 2010 (Table 2).

Table 3 presents, among elderly women and men, the values for life expectancy (LE), disability-free life expectancy (DFLE), disabled life expectancy (DLE) and proportion of years to be lived free of disability (DFLE % in LE).

In both genders, we observe an increase in DFLE in all age groups from 2000 to 2010. A decrease in DFLE % is also observed in LE, both among females and males, in all age groups (Table 3).

## DISCUSSION

The results showed that variations in disabled life expectancy and the proportion of years to be lived free of disability reveal a process of absolute and relative expansion

of morbidity (increase in DLE and decrease in DFLE percentage in overall LE) in progress among the elderly in the city of São Paulo between 2000 and 2010.

Historically, increased LE is accompanied by improvements in the population's health status. Today, however, this phenomenon no longer necessarily occurs in terms of overall impact on the morbidity of a population, because chronic diseases progressively replaced acute illnesses. Thus, the risk of illness is not only linked to the risk of dying, but also the risk of becoming disabled.<sup>27</sup> In this context, the time trends of LE and DFLE, considered together, can help to answer questions relating to population dynamics in terms of morbidity compression, expansion or balance.

Time series based on data from countries with low mortality rates (Western Europe, Nordic Countries, North America, Australia, Japan and New Zealand), covering a

**TABLE 2** Prevalence of disability by sex and age group. SABE<sup>1</sup> Survey, São Paulo, Brazil, 2000 - 2010

Age range (years)	2000 (%)	p	2010 (%)	p	Male	p	Female	p
	Male		Female		Male		Female	
60-64	15.79		36.83		23.65		40.7	
65-69	18.01		30.97		36.38		49.48	
70-74	22.13		37.44		38.26		43.47	
75-79	32.63		48.66		38.33		59.51	
≥ 80 years	43.62		54.72		47.86		68.46	
Total	21.79	<0.0000	39.02	0.5265	38.9	0.0003	54.33	0.0001

<sup>1</sup>available from: <http://www.fsp.usp.br/sabe>.

**TABLE 3** Life expectancy, disability-free life expectancy, disabled life expectancy and proportion (%) of years to be lived free of disability, by gender and age group. SABE Survey, São Paulo, Brazil, 2000 - 2010

Gender and age group	LE <sup>1</sup> (years)	DFLE <sup>2</sup> (years)	DLE <sup>3</sup> (years)	DFLE % in LE
	2000 / 2010	2000 / 2010	2000 / 2010	2000 / 2010
<b>Female</b>				
60-64	22.45 / 24.59	13.01 / 11.37	9.44 / 13.22	57.94 / 46.23
65-69	18.68 / 20.62	10.55 / 8.87	8.13 / 11.75	56.5 / 42.99
70-74	15.18 / 16.95	7.92 / 6.9	7.26 / 10.05	52.18 / 40.68
75-79	12.03 / 13.66	5.92 / 4.72	6.11 / 8.94	47.55 / 34.54
≥ 80 years	9.37 / 10.89	4.24 / 3.44	5.13 / 5.93	45.28 / 31.54
<b>Male</b>				
60-64	17.65 / 19.73	13.3 / 12.56	4.35 / 7.17	75.34 / 63.65
65-69	14.56 / 16.36	10.5 / 9.75	4.06 / 6.61	72.1 / 59.58
70-74	11.86 / 13.34	8.01 / 7.73	3.85 / 5.61	67.53 / 57.96
75-79	9.45 / 10.71	5.79 / 6.00	3.66 / 4.71	61.31 / 56.01
≥ 80 years	7.5 / 8.6	4.23 / 4.48	3.27 / 4.12	56.38 / 52.14

<sup>1</sup> life expectancy; <sup>2</sup> disability-free life expectancy; <sup>3</sup> disabled life expectancy.

period of 25 years, from 1970 to 1995, showed that the increase in LE at 65 years is universal and constant. The evolution of DFLE, in turn, seems to be stable, leading to the possibility that the years gained in LE may occur at the expense of disabled years.<sup>28</sup>

In the Global Burden of Disease Study, the analysis of healthy life expectancy for 187 countries over the period 1990-2010 showed that as life expectancy increases, the number of years of healthy life lost due to disability has also increased in most countries, including Brazil. This trend is consistent with the hypothesis of morbidity expansion.<sup>29</sup>

In Europe, however, time series obtained from 14 countries in the period 1995-2004, show important differences in the progression of a measure of healthy life expectancy called "healthy life years." Some countries show an increase in DFLE at 65 years or older (men: Austria, Belgium, Italy, Finland, Germany; women: Belgium, Italy, Sweden), while other countries show stagnation (men: France, Greece, Ireland, Spain; women: Austria, Denmark, UK, Finland, France, Spain) or reduction (men: Denmark, Portugal, Netherlands, Sweden, United Kingdom; women: Germany, Greece, Ireland, Netherlands, Portugal).<sup>28</sup>

In the United States of America (USA) for the last years of the twentieth century, using data from the Medicare Current Beneficiary Surveys (MCBS) of 1992-1996, Waidmann & Liu found a consistent decline in disability rates for instrumental activities of daily living, at 65 years of age or older.<sup>30</sup>

In face of these trend variations for DFLE in different countries, two hypotheses have been raised. First, the decrease in mortality was accompanied by redistribution of disability levels with, on the one hand, a reduction in the prevalence of the most severe level and, on the other hand, an increase in the prevalence of less severe levels. Thus, years of life in good self-perceived health have generally increased, while the trends in disabled life expectancy have evolved differently depending on the level of disability severity: with decrease for the most serious and increase for milder cases.<sup>28</sup>

Secondly, the disability that could be attributed to disease and aging would, in fact, be a consequence of limited education and training received by older generations. Among the variables that explain the variation in DFLE in different contexts, education has been highlighted as one of the most important. Analyses suggest that future changes in education levels would continue to contribute to improving the functionality of the populations.<sup>31</sup> A U.S. study showed by calculating DFLE between 1970 and 1990 that the compression of morbidity began

with individuals with more years of education.<sup>32</sup> A study from Austria about educational disparity trends showed that, among women, there is a significant increase of the difference in healthy life expectancy between people from middle- and low-education backgrounds.<sup>33</sup>

Thus, the results presented in this study need to be viewed with caution as the elderly population evaluated presented a lower level of education compared with countries where DFLE time series are available, such as those in Europe and North America. In populations with low educational levels, a tendency to expansion of morbidity would therefore be expected.

Moreover, we must also consider the fact that the disability measure used in the present study (basic activities of daily living) reflects a moderate to severe impairment of functionality. Unlike other countries where more severe disabilities have not increased over the years, this increase was found in the results presented. Since the most severe disabilities are less affected by education as a means of adaptation, these findings may suggest, in fact, a process of morbidity expansion in the Brazilian elderly population.

The self-reported information may also produce biases to the results. It is noteworthy, however, that studies on healthy life expectancy have worked with self-reported diagnoses.<sup>34,35</sup> Research in Brazil shows the validity of self-reported information to detect the health status. Conditions such as cardiovascular disease and diabetes seem to be properly reported by individuals, by virtue of the universal coverage offered by the Brazilian health system.<sup>36</sup>

A study based on the National Survey by Household Sampling (PNAD) from 1998 to 2003 also showed that the use of another respondent does not modify the distribution of self-rated health among the elderly, or the factors associated with it.<sup>37</sup>

Another aspect to be taken into account involves the non-inclusion of elderly patients treated in institutions, which could also lead to underestimation of the level of disability, to the extent that this elderly population could be experiencing higher prevalence of disability.

The fact that we worked with repeated cross-sectional data, using prevalence rates in accordance with the Sullivan method, has disadvantages when trying to think in terms of the changes that have been occurring in mortality and disability in the elderly population over time. Due to its simplicity, however, the life tables in several studies have been calculated based on the Sullivan method, which has been the technique most widely used in many countries, thus facilitating future comparisons.<sup>38,39</sup>

As research implications, it is considered that future studies could use longitudinal designs enabling better understanding of the transitions between health states, especially the functional capacity.<sup>38</sup> Studies including the institutionalized population could bring more information about the evolution of disabled life expectancy among the elderly. The use of the Disability-Adjusted Life Expectancy (DALE) indicator to compare the differences between genders and sub-populations with different levels of disability severity might bring new information about the differences in DFLE in the elderly population. Studies that address the relationship between multimorbidity and functional capacity may contribute to the understanding of the process of morbidity compression in this population.

According to the results of this study, the expansion of morbidity is an ongoing process in the elderly population in the municipality of São Paulo, for the period 2000-2010. Nevertheless, it has been shown that efforts to promote health in populations of young adults (aged 65 or less) can lead to improvements in health and longevity in the elderly, without increasing health expenditures.<sup>27</sup> In this sense, the health status seems to depend on public efforts to combat smoking, obesity, low levels of exercise, poor diet and excessive alcohol intake.<sup>40</sup>

Finally, we assume that a synergistic strategy to improve educational levels, improve nutritional status, improve working conditions and improve health behaviors could preventively lead to improved functional capabilities and performance in essential activities of daily life, contributing to the healthy life expectancy of future generations of elderly people.

## CONCLUSION

Variations in disabled life expectancy and in the proportion of years to be lived free of disability showed that the expansion of morbidity is an ongoing process in the elderly population in the municipality of São Paulo, from 2000 to 2010.

## RESUMO

A expansão da morbidade: tendências da expectativa de vida saudável da população idosa

**Objetivo:** analisar as mudanças na expectativa de vida (EV) e na expectativa de vida livre de incapacidade (EVLI) dos indivíduos idosos do município de São Paulo, de 2000 a 2010, de modo a avaliar a ocorrência de compressão ou expansão da morbidade nessa população.

**Métodos:** estudo transversal repetido, de base populacional, utilizando dados oficiais secundários para o município de São Paulo e dados obtidos a partir do Estudo Saúde Bem-Estar e Envelhecimento (SABE). A incapacidade funcional foi definida como dificuldade para a realização de pelo menos uma atividade básica de vida diária. O método de Sullivan foi utilizado para o cálculo de EV e EVLI para os anos de 2000 e 2010.

**Resultados:** de 2000 a 2010, observou-se um aumento da expectativa de vida com incapacidade (EVCI) em todas as faixas etárias, em ambos os sexos. A proporção de anos de vida livres de incapacidade, aos 60 anos, decresceu de 57,94% para 46,23% em mulheres, e de 75,34% para 63,65% em homens. Já aos 75 anos, esta proporção decresceu de 47,55% para 34,54% em mulheres, e de 61,31% para 56,01% em homens.

**Conclusão:** a expansão da morbidade é um processo em curso na população idosa do município de São Paulo, no período de 2000 a 2010. Os resultados apresentados podem colaborar para a elaboração de estratégias preventivas e para o planejamento de serviços de saúde adequados às futuras gerações de idosos.

**Palavras-chave:** esperança de vida; expectativa de vida ativa; tábuas de vida; morbidade; idoso.

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# Pregnancy-induced hypertension syndrome and cardiovascular risk

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## SUMMARY

**Objective:** to analyze the changes in life expectancy (LE) and disability-free life expectancy (DFLE) in São Paulo's elderly population to assess the occurrence of compression or expansion of morbidity, between 2000 and 2010.

**Methods:** cross-sectional and population survey, based on official data for the city of São Paulo, Brazil, and data obtained from the Health, Well-Being and Aging Survey (SABE). Functional disability was defined as difficulty in performing at least one basic activity of daily living. The Sullivan method was used to calculate LE and DFLE for the years 2000 to 2010.

**Results:** from 2000 to 2010, there was an increase in disabled life expectancy (DLE) in all age groups and both sexes. The proportion of years of life free of disability, at 60 years of age, decreased from 57.94% to 46.23% in women, and from 75.34% to 63.65% in men. At 75 years of age, this ratio decreased from 47.55% to 34.54% in women, and from 61.31% to 56.01% in men.

**Conclusion:** the expansion of morbidity is an ongoing process in the elderly population of the municipality of São Paulo, in the period 2000-2010. These results can contribute to the development of preventive strategies and planning of adequate health services to future generations of seniors.

**Keywords:** life expectancy, active life expectancy, life tables, morbidity, elderly.

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## INTRODUCTION

Cardiovascular diseases (CVD) are the leading cause of death in women and men in Brazil, accounting for about 20% of deaths in individuals over 30 years.<sup>1</sup> The difference in mortality between genders was noticed since the mid 1980s and, since then, occurrence has increased among women.<sup>2</sup>

Certain conditions during pregnancy increase the risk of hypertension, diabetes and atherosclerosis, resulting in a higher chance of coronary heart disease in women at a young age.<sup>2</sup> Among the pathological conditions that can compromise the normal course of pregnancy and have close relationship with these changes, the pregnancy-induced hypertension syndromes (PHS) are the entities most clinically relevant, being the leading cause of maternal and perinatal mortality in several studies in Brazil and worldwide.<sup>3,4</sup>

Recently, the relationship between the occurrence of a pregnancy complicated by hypertension and the development of future complications was assessed, focusing on cardiovascular disorders due to the magnitude and importance they tend to assume in the context of public health.<sup>5,6</sup>

The relationship between history of hypertension during pregnancy and the increased risk of CVD has been described in many studies whose results indicate PHS as a possible independent risk factor for cardiovascular disease, which deserves more attention when assessing the obstetric history of women, being even more important in the presence of traditional non-modifiable risk factors.<sup>6-8</sup>

This study sought to identify if the history of PHS is associated with changes in risk factors, morbidities and the occurrence of cardiovascular events (CVE), in the long

run, characterizing the profile of cardiovascular risk (CVR) calculated according to the Framingham Score (FRS).

## METHODS

This is a retrospective cohort study involving 60 women who gave birth in the Assis Chateaubriand Maternity School-UFC (MEAC) between 1992 and 2002 (mean follow-up of 15.2 years). MEAC, located in Fortaleza, state of Ceará, is a tertiary hospital with specialized care in medium- and high-risk pregnancies, which treats patients from the state capital and countryside.

The sample size was calculated assuming the prevalence of HBP at 27% and mean odds ratio at 19.3, according to a cohort study that assessed cardiovascular risk factors in women with history of pregnancy-induced hypertension syndrome, for a power of 90% and significance level at 5%, resulting in a sample of 30 patients in each group.<sup>9</sup>

The group of exposed subjects comprised 30 women with any of the PHS classifications (three with chronic hypertension simultaneous to index pregnancy, two with pregnancy-induced hypertension, nine with mild preeclampsia, 13 with severe preeclampsia, two with preeclampsia superimposed on chronic hypertension, and one with eclampsia), and the group of non-exposed individuals included 30 women without pathological obstetric history, randomly selected in the same perinatal period of the patients included in EG. One non-exposed patient was selected for each exposed. For diagnosis and classification of PHS, the patients' medical records were checked. The classification considered was that on the day of hospital discharge and not on the day of admission.

At the time of selection, the participants who experienced any other obstetric complications during index pregnancy, specifically multiple gestation, and those related to placental disorders, such as premature placental detachment and placenta previa, were excluded, as well as those with conditions knowingly related with future cardiovascular risk, such as gestational diabetes. At the time of the risk assessment, those who were pregnant or in the postpartum period were excluded.

Patients selected in the first stage were invited for a clinical assessment via an invitation letter, home visit and/or telephone contact explaining all of the objectives of the study, the exams to be conducted and emphasizing their freedom to accept participation in the study or otherwise, without damages or loss. If they agreed, and after signing the informed consent form, an assessment was scheduled for evaluation of current clinical and obstetri-

cal variables, anthropometric assessment and laboratory assessment. The assessment of cardiovascular risks was conducted between March and September 2012.

The information collected in the medical records was checked with the patient and other up to date information was sought. Risk information before and after the index pregnancy was evaluated: age, race, parity, marital status, occupation, education level, family income, current obstetric history, smoking habits, current illnesses, practice of physical activity and family history of CVD (confounding variables), and also occurrence of CVE, current morbidity and use of medication (dependent variables).

Other dependent variables were assessed in the physical exam: measuring of systolic blood pressure (SBP) and diastolic blood pressure (DBP) with the use of the semiautomatic monitor *MicroLife BP 3BTO-H*, according to the recommendations of the VI Brazilian Hypertension Guideline,<sup>10</sup> weight and percentage of body fat assessments using a bioimpedance technique with the digital body analyzer scale *Wiso W835*, calculation of the Body Mass Index (BMI) in accordance with the Brazilian Obesity Guidelines 2009/2010,<sup>11</sup> waist (WC), abdominal (AC) and hip circumference (HC) measurements for calculation of the following anthropometric ratios: waist to hip ratio (WHR), waist to height ratio (WHtR) and conicity index (C index), determined using the formula described by Valdez.<sup>12</sup>

Total cholesterol and fractions of HDL, LDL and VLDL, triglycerides, AST and ALT, urea and creatinine and fasting glucose were analyzed. Patients were advised to fast for 12 hours and abstain from alcohol one day before collecting blood. The Tindler enzymatic method was used to analyze the samples of total cholesterol and fractions and triglycerides, while the enzymatic method was used for the fasting glucose analysis, the Jaffe method for creatinine analysis and the UV kinetic method for evaluation of AST and ALT measurements.

The cardiovascular risk was also assessed using the Framingham Risk Score, given its globally recognized validity, using the variables of age, LDL-C, HDL-C, blood pressure, presence of diabetes and smoking habits. The risk of cardiovascular events occurring in 10 years is estimated using the total points for each factor. The revised Framingham Score for women was used.<sup>13</sup>

The data collected was tabulated and analyzed using the Statistical Package for Social Sciences for Personal Computer (SPSS-PC) software, version 18.0 with calculation of averages and standard deviations (SD) for analysis of the clinical and metabolic variables. The Kolmogor-

rov-Smirnov test was used to test the normality of the variables, while the Student's t-test was used to compare the variables with the normal distribution, and the Mann-Whitney test for variables that were not normally distributed. Fisher's exact test was used for qualitative variables. Statistical significance was considered when the value of  $p < 0.05$ , with a confidence interval (CI) of 95%. The odds ratio was calculated for the variables that were statistically significant in the first analysis.

The project was approved by the Research Ethics Committee/MEAC under Report n°83/11.

## RESULTS

The groups did not differ in terms of age, parity, family history of CVD, race, smoking habits, physical activity or menopause.

Age at the time of delivery varied from 15 to 43 (average of  $26.2 \pm 7.7$ ) years, and at the time of the risk assessment varied from 28 to 61 (average of  $41.3 \pm 8.8$ ) years.

The patients did not differ in terms of prior obstetric history at index pregnancy in relation to the number of pregnancies ( $2.2 \pm 2.3 \times 3.0 \pm 4.1$ ;  $p = 0.78$ ), parity ( $1.0 \pm$

$1.9 \times 1.2 \pm 2.7$ ,  $p = 0.26$ ) and number of abortions ( $0.2 \pm 0.4 \times 0.8 \pm 1.9$ ;  $p = 0.25$ ).

The number of years in school varied between zero and eleven years ( $6.9 \pm 3.1 \times 6.8 \pm 3.9$ ;  $p = 0.91$ ). Education level was not different between groups. Family income calculated using the number of minimum salaries varied between 0.5 and 3 ( $1.5 \pm 0.6 \times 1.5 \pm 0.7$ ;  $p = 1.00$ ). Family income showed no difference between the groups, either.

Table 1 presents the current clinical history of the patients collected via anamnesis during a clinical visit.

The diagnosis of at least one morbid condition was informed by 40% of the women, showing a trend for a greater number of women with a diagnosis in the group of exposed patients.

High Blood Pressure (HBP) was the most frequent in both groups, having been cited by 15 (25%) of patients in association with other pathologies or otherwise. Type 2 *diabetes mellitus* (DM) was the second most reported disease, with eight cases (13.3%). Dyslipidemias also occupied a significant number of cited cases, accounting for 13.3% of cases.

**TABLE 1** Current long-term medical history of women with (EG) and without pregnancy-induced hypertension (NEG). MEAC-UFC. Fortaleza, 2012

	Exposure				p*
	Non-exposed		Exposed		
	n	%	n	%	
<b>Current diseases diagnosed/undergoing treatment</b>	8	26.7	16	53.3	0.06*
<b>Disease classification**</b>					
HBP	2	6.7	13	43.3	-
DM	1	3.3	7	23.3	
Dyslipidemias	2	6.7	6	20	
<b>Occurrence of admissions</b>	9	30	9	30	1.00*
<b>Occurrence of CVE***</b>	-	-	3	10	0.23**
<b>Family history of CVD/CVE**</b>	25	86.2	29	96.7	0.19**
<b>Classification of the family history of CVD/CVE**</b>					
HBP	22	75.8	21	70	-
DM	7	24.1	14	46.6	
AMI	4	13.8	7	23.3	
Stroke	5	17.2	7	23.3	
<b>Use of medication</b>					
Antihypertensive	3	10	11	36.7	0.03**
Hypoglycemic	1	3.3	7	23.3	0.05**
Anticoagulant	1	3.3	2	6.7	1.00**
Fibrates/statins	1	3.3	4	13.3	0.35**
Hormonal contraceptives	1	3.3	4	13.3	0.35**

\* Different statistical tests were used in the analysis: \*X<sup>2</sup> test; \*\*Fisher's test.

\*\* The patients cited one or more pathologies.

\*\*\* HBP: high blood pressure; DM: diabetes mellitus; AMI: acute myocardial infarction; CHF: congestive heart failure; CVE: cardiovascular event; CVD: cardiovascular disease.

In relation to the occurrence of cardiovascular events, three cases were documented among the 60 patients assessed (5%), all of which occurred in patients from the exposed group. In relation to the classification, the occurrence of one case of deep vein thrombosis was reported, and two cases of cerebrovascular accidents. There was no statistically significant difference between the groups in relation to the occurrence of CVE.

After taking history of medication use by patients, we found a statistically significant difference in the use of antihypertensive and hypoglycemic medication, with a trend towards a difference between the groups. These medicines are used to treat the illnesses cited most by the patients in the study, with 23.3% of the sample reporting the use of an-

ti-hypertensive medication and 13.3%, the use of hypoglycemic medication. The OR was calculated for the use of anti-hypertensive medication, with a score of 5.2 (95CI: 1.3-21.2).

Table 2 presents the clinical and metabolic variables related to an unfavorable cardiovascular profile, with averages and standard deviations for each group.

The weight of the patients analyzed varied between 45 and 99.9 kg with a mean of 70.4 ± 12.5 kg, and no statistically significant difference between the patients.

The BMI assessment showed a statistically significant difference between the groups, with values between 19.7 and 46.9 kg/m<sup>2</sup> and a mean of 29.9 ± 4.9. The highest BMI values were found in the exposed group. The OR calculation was 1.13 (95CI: 1.00-1.3).

**TABLE 2** Long-term clinical and metabolic characterization of women with (EG) and without pregnancy-induced hypertension (NEG). MEAC-UFC. Fortaleza, 2012

Clinical and metabolic characteristics	Exposition		p*
	Non-exposed	Exposed	
<b>Anthropometric variables</b>			
Weight (kg)	68.6±9.5	72.3±14.8	0.25*
Height (m)	1.54±0.1	1.52±0.1	0.06*
BMI (kg/m <sup>2</sup> )	28.5±3.2	31.2±5.9	0.03*
SBP (mmHg)	119.4±14.3	129.9±22.1	0.03*
DBP (mmHg)	78.9±11.3	83.5±15.0	0.19*
AC (cm)	93.1±9.8	97.2±12.4	0.16*
WC (cm)	86.5±8.6	89.1±11.8	0.32*
HC (cm)	102.7±8.3	106.9±11.1	0.10*
WHR	0.8±0.1	0.8±0.1	0.63*
C Index	1.2±0.1	1.2±0.1	0.84*
WHtR	0.6±0.1	0.6±0.1	0.12*
Biceps skin fold (mm)	13.1±5.3	15.6±8.7	0.19*
Body fat (%)	42.9±6.1	42.4±7.5	0.75*
<b>Metabolic variables</b>			
Total cholesterol	177.6±40.1	191.6±30.8	0.13*
Triglycerides	143.4±97.5	155.1±73.3	0.60*
LDL-c cholesterol	104.7±31.4	124.0±28.4	0.02*
HDL-c cholesterol	42.2±11.1	39.9±10	0.40*
VLDL-c cholesterol	28.2±20.1	30.2±12.9	0.66*
AST	35.6±14.2	28.2±6.9	0.01*
ALT	30.2±15.2	23.8±7.9	0.06*
Urea	25.1±7.4	22.4±6.5	0.16*
Creatinine	0.7±0.1	0.8±0.3	0.17*
Fasting glucose	96.5±9.9	121.1±59.3	0.02**

\*Different statistical tests were used in the analysis: \*Student' t-test; \*\*Mann-Whitney.

BMI - Body Mass Index; SBP - systolic blood pressure; DBP - diastolic blood pressure; AC - abdominal circumference; WC - waist circumference; HC - hip circumference; WHR - waist to hip ratio; C Index - conicity index; WHtR - waist to height ratio; LDL-c - Low Density Lipid; HDL-c - High Density Lipoprotein; VLDL-c - Very Low Density Lipoprotein; AST - aspartate transaminase; ALT - alanine aminotransferase.

SBP was also shown to be significantly different between the groups, with values between 88 and 192 mmHg and a mean of  $124.6 \pm 19.1$  mmHg. The patients in the exposed group presented higher average SBP values. The OR calculation was 1.03 (95CI: 1.00-1.06).

DBP varied between 56 and 111 mmHg, with a mean of  $81.2 \pm 13.3$  mmHg, and no statistically significant difference between the groups.

The waist (WC), abdomen (AC) and hip circumference (HC) measurements were taken. The WC measurements varied between 64 and 115 cm and presented a mean of  $87.8 \pm 10.3$  cm. The AC measurements varied between 69 and 119 cm, with a mean of  $95.2 \pm 11.2$  cm. The HC measurements varied between 82 and 133 cm, with a mean of  $104.7 \pm 9.9$  cm. None of these presented a statistically significant difference between groups.

The following anthropometric ratios were calculated: waist to hip ratio (WHR), C Index and waist to height ratio (WHtR), with WHR values found varying between 0.70 and 0.97 with a mean of  $0.8 \pm 0.1$  in the sample. The C Index varied between 1.00 and 1.39, with a mean of  $1.2 \pm 0.1$ . The WHtR presented a greater variation between the groups, varying between 0.42 and 0.79m with a mean of  $0.6 \pm 0.1$ . There was no significant difference for the three parameters analyzed above.

There were statistically significant differences for the values of the LDL portion of the cholesterol and fasting glucose, with higher values in the group of exposed patients. The LDL-c measurement varied between 50.2 and 189 mg/dL with a mean of  $113.5 \pm 31.3$ . Fasting glucose varied between 75 and 339 mg/dL with a mean of  $108.8 \pm 43.9$ . An OR for LDL-c of 1.02 was found (95CI: 1.00-1.04) while for fasting glucose the OR was 1.03 (95CI: 1.00-1.07).

The total cholesterol values found in the sample varied between 115 and 276 mg/dL, with a mean of  $184.5 \pm 36.1$  mg/dL. The triglyceride values varied between 32 and 413 mg/dL with a mean of  $149.3 \pm 85.7$  mg/dL while the HDL-c varied between 25 and 70 mg/dL with a

mean of  $41.1 \pm 10.6$  mg/dL. There was no significant difference for the three parameters analyzed above.

The Framingham Risk Score was used for the cardiovascular risk assessment, estimating the risk of cardiovascular events in 10 years. Table 3 presents the scores relating to the Framingham Score calculation and the high and low risk categorization based on this score.

The Framingham Score varied in relation to scores with values between -7 and 22 with an average of  $5.5 \pm 6.6$ . The OR for the Framingham Score was 1.09 (95CI: 1.00-1.19).

Three patients (5%) presented high cardiovascular risk, all in the exposed group; however, this variable was not statistically significant between the groups. When the frequency of low risk classification for CVE, characterized as a risk of less than 10%, was analyzed a statistically significant difference was found between the groups, with all of the patients from the non-exposed group included in this classification. Only two patients were classified as having an intermediate risk (3.3%), characterized as a risk between 10 and 20%.

## DISCUSSION

The groups of patients analyzed were similar in terms of baseline characteristics in the period they started being monitored in relation to age, number of pregnancies, parity, abortions and smoking habits, factors which could cause a differentiated cardiovascular risk for age and smoking status are factors that affect the risk of CVE. Results of current studies present a differentiated cardiovascular profile for multiparous women and women with a history of consecutive abortions.<sup>14,15</sup>

In relation to current clinical history, the groups showed differentiated profiles for morbidity and use of medication, with the group of exposed patients holding a more unfavorable morbidity profile when compared to the non-exposed group.

Hypertension assumes a prominent role among the group of morbidities stated, with a frequency higher than expected for the general population found in this study.

**TABLE 3** Long-term characterization of cardiovascular risk using the Framingham Score in women with (EG) and without pregnancy-induced hypertension (NEG). MEAC-UFC. Fortaleza, 2012

	Exposition		p*
	Non-exposed	Exposed	
Framingham score	3.7 ± 6.1	7.5 ± 6.8	0.03*
Low risk for CVE (n,%)	30 (100%)	24 (80%)	0.02**
High risk for CVE (n,%)	-	3 (10%)	0.11**

\*Different statistical tests were used in the analysis: \*Student' t-test; \*\*Fisher's test. CVE - cardiovascular event; CVR - cardiovascular risk.

One study found a prevalence of 22.7% for HBP, a lower value than that presented in our study.<sup>16</sup>

One study found that among 191 analyzed women with a history of PHS, 32.5% were hypertensive 21 years after the birth, a lower result than that found in this study, which presented a frequency of 43.3% in the group of exposed patients.<sup>17</sup>

The study found different relative risks for occurrence of HBP in women with a history of PHS depending on its seriousness. For women with a history of pregnancy-induced hypertension syndrome (PHS), the RR was found to be 2.47 while for preeclampsia/eclampsia (PE/E) the RR was 3.89.<sup>7</sup>

The frequency of DM and dyslipidemias in treatment was also shown to be important in our study, with two conditions reported by 13.3% of patients. In the group of exposed patients, DM was reported by 23.3%, a high frequency considering that presented in a national study, with a prevalence of 3.7% for diabetes mellitus.<sup>16</sup>

Analyzing the association between hypertensive disorders and the risk of maternal cardiovascular morbidity and type-2 diabetes after follow-up for an average of 14.6 years, one study found that women with pregnancy-induced hypertension presented a risk 3.12 times higher for type 2 DM diagnosis, and in those with PE the risk was 3.68 times higher.<sup>6</sup>

The use of medication was also statistically significant when comparing the history of women with PHS and without exposure, but with a less striking risk gradient than that observed for the occurrence of hypertension. Women with a history of PHS presented RR of 1.89 and women with a history of PE/E had an RR of 1.90 for the use of medication.<sup>7</sup>

The literature is vast in pointing out that women with a history of PHS tend to present greater frequencies of hypertension and DM diagnoses and the use of antihypertensive and hypoglycemic medications.<sup>6,7,18</sup>

The small number of cases of CVE did not enable a significant difference to be found between the groups, but draws attention to the fact that all cases found occurred in patients with a history of PHS.

Various studies evaluating CVE such as outcomes of the follow-ups of women with a history of PHS indicate a higher frequency of such events in this group.<sup>6,18,19</sup>

The practice of physical exercise was not shown to be different between the groups, with a low frequency of physical activity found in the sample studied. These results are comparable with the study which verified that the majority of women interviewed (68%) did not practice physical activity.<sup>20</sup>

In relation to the clinical and metabolic assessment of the patients, important differences were found, which are significant to assessing the cardiovascular risk profile, the main objective of the assessment. The BMI was found to be significantly different in women with a history of PHS, data which has already been presented in other studies.<sup>5,21</sup>

A study that analyzed 40 women with a history of PHS and 14 with a history of normotensive pregnancies, after a follow-up period of 14.6 years in the exposed group and 15.9 years in the non-exposed group, found higher BMI, AC and DBP values in women with a history of PHS, with a mean BMI of  $29.96 \pm 6.13$  kg/m<sup>2</sup>, AC of  $93.15 \pm 12.31$  cm and DBP of  $82 \pm 11.86$  mmHg in the exposed group ( $p = 0.019, 0.026$  and  $0.047$ , respectively).<sup>5</sup>

In our study, the mean BMI measurements in the two groups were higher than those found in this study<sup>5</sup>, demonstrating an even more unfavorable profile in this sample in relation to excess weight/obesity, which was found in 90% of the sample, drawing attention to the fact that class 2 and 3 obesity were only found in patients with a history of PHS. Another study found a prevalence of 47.7% for excess weight and obesity in women from São Leopoldo, state of Rio Grande do Sul (Brazil).<sup>16</sup>

Studies indicate that excess weight and obesity represent a serious health risk and are strongly associated with an increased risk of cardiovascular diseases, type 2 diabetes mellitus and metabolic disorders.<sup>22</sup>

One study that evaluated 168 pairs of women recruited between 1989 and 1997, 7.8 years after delivery, 105 of which had a history of PHS and 63 with a history of PE, found higher average BP in patients with a history of PHS, with mean SBP values equal to 115 mmHg, lower than those presented by the patients in this study ( $129, \pm 22.1$  mmHg).<sup>21</sup>

Fraser et al.<sup>23</sup> found that approximately 20 years after pregnancy, women with a history of PHS or PE presented higher BMI, WC and BP when compared with women with a history of normotensive pregnancies. The authors also found altered pressure values upon the birth of SGA infants.

The AB and WC measurements, important parameters in the evaluation of central obesity<sup>24</sup> had higher means than the value considered appropriate according to national consensus; however, this difference was not significant between groups.<sup>11,25</sup>

The accumulation of fat in women in the region of the trunk and abdomen is related to changes occurring in recent decades relating to dietary and lifestyle habits, which could indicate an increasingly higher exposure to cardiovascular risks.<sup>24</sup>

In addition to isolated anthropometric measurements, three important anthropometric ratios were analyzed (WHR, C Index and WHtR) already described in the literature in relation to their effectiveness in identifying the differentiated cardiovascular risk profile.<sup>24,26,27</sup>

In this study, none of the ratios showed difference between the groups evaluated, with only the C Index and WHtR displaying higher values than recommended as cut-off points for the assessment of cardiovascular risk in women.<sup>26,27</sup>

Analyzing the blood chemistry characteristics, an unfavorable lipid profile was found in the exposed sample, where the measurements of LDL cholesterol were higher, which is concerning given that this portion of cholesterol is related with an unfavorable cardiovascular risk profile in the general population. The study found lower average LDL-c in the sample studied ( $120.7 \pm 33.2$ ), with no statistically significant difference between the groups in relation to this measurement.<sup>5</sup>

The measurements of the average total cholesterol, triglycerides and VLDL were higher in the exposed group; nevertheless, the differences were not found to be statistically significant, unlike the results of other studies showing a completely altered lipid profile in patients with a history of PHS.<sup>21</sup> The small sample may have been responsible for the lack of statistical significance in relation to these values.

In both groups, the mean values for HDL-c portion were lower than the value recommended by national consensus as ideal parameters for the female population, being the second most altered measurement in the sample studied (75.9%). The fraction of HDL cholesterol includes actions that contribute to protection of the vascular bed against atherogenesis, such as the removal of oxidized lipids in LDL, inhibition of attachment of adhesion molecules and monocytes to the endothelium and stimulation of nitric oxide release. Therefore the reduction in the levels of this portion of cholesterol, an abnormality demonstrated in other studies, is troublesome.<sup>28</sup>

The difference in fasting glucose was statistically significant, with exposed patients presenting the highest averages. When analyzed for their adequacy in terms of the parameters considered as normal for evaluation of diabetes, all patients with values above that recommended by the Brazilian Diabetes Society,<sup>11</sup> i.e., 126 mg/dL, were allocated to the exposed group.

Regarding the cardiovascular risk profile calculated using FRS, the study showed that 16% of women with a

history of PHS had Framingham risk scores 30% higher than women with a history of normotensive pregnancies, even after adjustment for pre-pregnancy BMI. The authors believe that the explanation for the entire cohort being assessed as a low risk profile for CVE resides in the young age of the patients in the study, having found an average risk of 3%, with evidence of variations related to complications during pregnancy.<sup>23</sup>

In this study, we only found five patients in the sample (8.5%) with an unfavorable cardiovascular risk profile according to the Framingham Score. Even in small numbers, the occurrence of an unfavorable risk profile for CVE (intermediate or high) in the exposed group indicates the need for research with larger samples in these groups, temporally assessing the modification of this risk according to exposure.

The body of evidence published so far demonstrates the need for a differentiated clinical attention for patients with a history of PHS, encouraging more specific and earlier reviews in this group of patients, with postpartum and long-term follow-up focusing on the prevention of cardiovascular events.

Despite the clear association with an increased risk in patients with a history of PHS, due to the similarity between the groups regarding other risk factors for CVD, the findings should be interpreted with caution. The number of patients can be considered small. It was difficult to find many of the patients owing to changes of address and phone numbers, and a considerable number refused to participate. Although random, there may have been a selection of cases very similar to the controls, which may also have contributed to the identification of few differences for the risk assessments.

The analysis was able to provide a relatively long follow up, which should be considered very positive. However, follow up times with longer monitoring periods are needed, especially after the implementation of protective measures to investigate whether the risk can be modified or be considered as unchanging, similar to a family history of CVD. That is, there is still doubt as to whether PHS is an event associated with increased risk of CVE alone or if this increased risk is only associated with other factors that it causes: increased central obesity, metabolic syndrome, hyperglycemia, and hypertension.

Further investigations should be made into the relationship between the severity of PHS and its recurrence with the severity of interference in cardiovascular risk, and the association with other sexual and reproductive factors, inclu-

ding isolated and joint adverse perinatal outcomes. The ideal would be to assess the real value of each obstetric factor (e.g. prematurity, low birth weight and fetal growth restriction) on the risk of the development of future CVE.

## CONCLUSION

The study showed an unfavorable cardiovascular risk profile in patients with a history of PHS, demonstrated through changes in anthropometric measurements such as BMI and WC, as well as metabolic measurements, such as the lipid profile (LDL-c cholesterol), and glycemic measurements (fasting glucose), even in patients considered young for the prevalence of such conditions. The patients in the exposed group presented higher Framingham Risk Scores.

## RESUMO

Síndrome hipertensiva gestacional e risco cardiovascular.

**Objetivo:** caracterizar o perfil de risco cardiovascular em longo prazo de mulheres com história de síndrome hipertensiva da gestação (SHG) e compará-lo ao de mulheres com histórico de gestação normotensa.

**Métodos:** este é um estudo de coorte retrospectivo que incluiu 60 mulheres que deram à luz na MEAC-UFC entre os anos de 1992 e 2002 (seguimento médio de 15,2 anos). O grupo de exposição (GE) foi composto por 30 mulheres em qualquer categoria de SHG, e o grupo de não exposição (GNE) compreendeu 30 mulheres sem história de patologia obstétrica. Foram avaliados os dados antropométricos e laboratoriais associados ao risco cardiovascular e calculados o escore Framingham (variáveis dependentes). Para variáveis quantitativas, foram usados o teste t de Student e o teste de Mann-Whitney. Para variáveis qualitativas, aplicou-se o teste exato de Fisher. Considerou-se a significância estatística como  $p < 0,05$ .

**Resultados:** GE apresentou valores mais altos de IMC ( $p=0,03$ , OR=1,13, IC 1,00-1,3), PAS ( $p=0,03$ , OR=1,03, IC 1,00-1,06), LDL-C ( $p=0,02$ , OR=1,02, IC 1,00-1,04) e glicose de jejum ( $p=0,02$ , OR=1,03, IC 1,00-1,07), além de valores mais altos no escore de Framingham ( $p=0,03$ , OR=1,09, IC 1,00-1,19). As mulheres em GE usaram medicamentos anti-hipertensivos com mais frequência ( $p=0,03$ , OR=5,2, IC 1,3-21,2).

**Conclusão:** foi encontrado um perfil de risco cardiovascular desfavorável nas pacientes com história de SHG em comparação com as mulheres sem esse histórico.

**Palavras-chave:** pré-eclâmpsia; hipertensão induzida pela gravidez; doenças cardiovasculares; fatores de risco; epidemiologia.

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# Prenatal diagnosis of congenital rubella infection in São Paulo

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## SUMMARY

**Objective:** rubella during the early stages of pregnancy can lead to severe birth defects known as congenital rubella syndrome (CRS). Samples collected from pregnant women with symptoms and suspected of congenital rubella infection between 1996 and 2008 were analyzed.

**Methods:** a total of 23 amniotic fluid samples, 16 fetal blood samples, 1 product of conception and 1 placenta were analyzed by serology and RT-PCR.

**Results:** all patients presented positive serology for IgG / IgM antibodies to rubella virus. Among neonates, 16 were IgG-positive, 9 were IgM-positive and 4 were negative for both antibodies. Of the 25 samples analyzed in this study, 24 were positive by RT-PCR. Changes in ultrasound were found in 15 (60%) of 25 fetuses infected with rubella virus. Fetal death and miscarriage were reported in 10 (40%) of the 25 cases analyzed. The rubella virus was amplified by PCR in all fetuses with abnormal ultrasound compatible with rubella. Fetal death and abortion were reported in 10 of 25 cases analyzed.

**Conclusion:** this study, based on primary maternal rubella infection definitely confirms the good sensitivity and specificity of RT-PCR using amniotic fluid and ultrasound. The results showed that molecular assays are important tools in the early diagnosis of rubella and congenital rubella syndrome.

**Keywords:** ultrasonography, prenatal, rubella syndrome, congenital, amniotic fluid, diagnosis, RT-PCR, serology.

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## INTRODUCTION

Rubella virus (RV) usually causes a mild exanthematous disease frequently accompanied by adenopathy and occasional arthralgia. However, infection during pregnancy, particularly during the first trimester, can lead to severe birth defects known as congenital rubella syndrome (CRS).<sup>1</sup> Congenital rubella infection causes fetal death and a spectrum of birth defects known as congenital rubella syndrome. The syndrome affects multiple organ systems and common abnormalities include deafness, congenital heart disease, cataracts and mental retardation.<sup>2</sup> Traditionally, detection of fetal viral infection relies on isolation and culture of virus or maternal and cord blood seroconversion.<sup>3</sup> Viral culture and subsequent identification from mother and fetuses and/or amniotic fluid has been the gold standard. This method is slow, taking between 1 to 3 weeks to

obtain a positive result. Maternal serology may also lack sensitivity and can be difficult to interpret. Advances in diagnostic techniques such as the polymerase chain reaction (PCR) allows rapid detection and it is a highly sensitive method. Recently, the diagnosis of congenital rubella infection is based mainly on the detection of rubella virus in amniotic fluid (AF) by RT-PCR<sup>4,5</sup> or detection of rubella virus specific IgM antibody in fetal blood.<sup>6,7</sup>

Rapid and accurate identification of the causative virus is increasingly important and can guide prenatal management as well as identify the need for long-term follow-up. In addition, in many countries, clinically recognized maternal rubella during the first 8 weeks of gestation is an indication for therapeutic abortion due to the high incidence of congenital defects. This is why there are only

a few PD studies in which rubella RNA is available. Infection prior to conception does not present a risk to the fetus, but when primary rubella infection occurs in the first 12 weeks of pregnancy, rubella virus will cross the placenta and induce generalized and persistent fetal infection in about 80% of cases.<sup>3,8</sup> Spontaneous abortion may take place in up to 20% of cases when rubella occurs in the first 8 weeks of pregnancy.<sup>9,10</sup> During the past 10 years, nationwide epidemics of rubella occurred approximately every 5 years in São Paulo, Brazil, namely in 1995, 2000 and 2007.<sup>1,11</sup> To reduce rubella transmission and prevent CRS, a nationwide campaign to vaccinate women and men against rubella was initiated in Brazil in 2001 and 2008. The World Health Organization (WHO) has estimated that more than 100,000 cases of CRS occur in developing countries every year; this represents a considerable social and economic burden. This study presents a series of CRI cases based on an integrated analysis of clinical features, serological and molecular investigation. Furthermore, all cases were submitted to clinical and laboratory analyses and a complete follow-up involving neonatal care in pediatric units by otorhinolaryngologists, ophthalmologists and cardiologists was carried out, thus providing a unique opportunity for the study of intrauterine transmission of rubella and its consequences to the fetus and newborn.

## METHODS

### Patients

Forty patients with abnormal ultrasound findings, clinical signs and serological evidence of rubella, were studied prospectively between 1996 and 2008 at the Fetal Medicine Unit, University of São Paulo. No termination of pregnancy was performed since Brazilian law does not allow it. Maternal age from 16 to 39 years (mean: 25 years). Gestational age at the time of acute rubella was based on the last menstrual period (LPM) and the first trimester ultrasound scan using the crown-rump length measurement. The diagnostic strategy was based on seroconversion and/or the detection of rubella virus-specific IgM. Newborn follow-up was based on the presence of structural malformations, rubella antibodies at birth and at 3 months of age, echocardiographic alterations, brainstem evoked response audiometry, and ophthalmic pathology. Among the pregnant women, 20 had symptoms, 15 had fever, exanthema and lymphadenopathy; 2 had fever and exanthema, and 3 had exanthema and lymphadenopathy. This study was previously submitted to and approved by the Ethics Committee on Research with Human Beings at University of São Paulo (623/CEP).

### Samples

The first maternal serum had been collected in the Clinical Hospital of the University's School of Medicine and the second sample after 15 days of the first collection. Newborn samples were obtained from umbilical cord blood at 3 months of age. Amniocentesis was offered to all 40 patients with clinical signs of rubella before 12 weeks of gestation, but only in 23 cases, amniocentesis was performed. The samples were obtained at 21 weeks of gestation and 6 weeks after the onset of clinical signs of rubella. A total of 23 amniotic fluid samples, 16 fetal blood samples, 1 product of conception and 1 placenta were analyzed (Table 1). All samples were stored at -80°C until use.

### Serological assays

Detection of IgG and IgM specific antibodies to rubella virus was performed using a commercial enzyme immunoassay (Siemens, Marbuy, Germany) according to the manufacturer's instructions.

### RNA extraction and reverse transcription

Viral RNA was extracted either directly from clinical specimens or from viral culture. Samples (200 µL) and inoculated cell cultures (300 µL) were extracted using Tri reagent (Molecular Research Center, Inc., Cincinnati, OH, USA) according to the manufacturer's protocol. Placental tissue was processed using the viral RNA Mini Kit (Invitrogen™ Life Technologies, Carlsbad, CA, USA). RV RNA was detected by RT-PCR as described previously.<sup>4</sup> The expected lengths of RT-PCR products synthesized using R2 and R7 (nt 8807–8991) and R11 and R8c (nt 8826–8968) primer pairs were 185 and 146 bp, respectively. All reactions were performed using positive and negative controls.

## RESULTS

### Maternal and newborn serology

All pregnant women studied had positive serology results for IgG and IgM to rubella virus in the first or second sample (Table 1). In 5 of the subjects, a second sample could not be collected (np). Of the 16 newborns that had serum samples, 11 (68,75%) were IgM-positive and 5 (31,2%) were IgM-negative. Serology could not be performed in 9 of the newborn due to fetal death or miscarriage.

### RT-PCR

Of the 25 samples analyzed in this study, 24 were positive by RT-PCR. The amniotic fluid samples negative on RT-PCR were confirmed by virus isolation. As a control,

**TABLE 1** Serological and PCR analysis in 25 pregnant women and newborn and outcome

		Pregnant						Newborn		
Case/year	Gestational of week symptom	Serology				RV detection		IgM	IgG	Outcome
		IgM		IgG		Sample	RT-PCT			
		1° sample	2° sample	1° sample	2° sample					
01/1996	11.2	pos	pos	neg	pos	AF	pos	pos	pos	Live
02/1996	11.9	pos	pos	neg	pos	AF	pos	pos	pos	Live
03/1996	10.9	pos	pos	neg	pos	AF	pos	pos	pos	Live
04/1996	11	pos	pos	neg	pos	AF	pos	pos	pos	Live
05/1998	11.5	pos	pos	pos	pos	AF	pos	pos	pos	Live
06/1999	11.4	pos	pos	pos	pos	AF	pos	pos	pos	Live
07/1999	12.0	pos	pos	neg	pos	AF	pos	np	np	Miscarriage
08/2000	4.4	pos	np	pos	np	AF	pos	np	np	Fetal death
09/2000	7.5	neg	pos	neg	pos	AF	pos	pos	pos	Live
10/2000	4.1	pos	neg	pos	pos	AF	pos	np	np	Fetal death
11/2000	11.2	neg	pos	neg	pos	AF	pos	pos	pos	Live
12/2000	1.4	pos	np	pos	np	AF	pos	np	np	Fetal death
13/2000	11.4	pos	pos	pos	pos	AF	pos	pos	pos	Live
14/2000	2	pos	pos	pos	pos	AF	pos	np	np	Fetal death
15/2000	5	pos	np	pos	np	AF	pos	np	np	Fetal death
16/2000	11.4	neg	pos	neg	pos	AF	pos	neg	pos	Live
17/2000	11.7	pos	pos	neg	pos	AF	pos	pos	pos	Live
18/2000	8.2	pos	pos	pos	pos	AF	pos	neg	pos	Live
19/2000	10.8	pos	neg	pos	pos	AF	pos	neg	pos	Live
20/2000	10.3	pos	pos	neg	pos	AF	pos	neg	neg	Miscarriage
21/2001	7.4	pos	neg	pos	pos	AF	pos	np	np	Fetal death
22/2001	11.5	pos	neg	pos	pos	AF	pos	pos	neg	Live
23/2001	4.5	pos	pos	pos	pos	AF	neg	neg	pos	Live
24/2002	4	pos	pos	np	np	POC	pos	np	np	Fetal death
25/2008	12	pos	pos	pos	np	Placenta	pos	np	np	Fetal death

pos: positive; neg: negative; POC: product of conception; AF: amniotic fluid; np: no processed

the 25 samples in this study were submitted to PCR for other viruses such as parvovirus B19, herpes virus simplex 1 and 2, and cytomegalovirus. Twenty-four samples were negative for these viruses, only one (case 23) was positive for cytomegalovirus.

**Evaluation of ultrasound**

Alterations were found in several follow-up evaluations by ultrasound in 15 (60%) of the 25 fetuses infected with rubella virus. Miscarriage and fetal death were reported

in 10 (40%) of the 25 cases analyzed (Table 2). Rubella virus was amplified by PCR in all fetuses showing ultrasound alterations compatible with rubella: growth restriction, hepatomegaly, hydrocephaly, ventricular septal defect, intracranial calcifications, oligohydramnios, with more than one abnormality in some cases (Table 2). Although rare in congenital rubella, in one case (case 7) the cranial cap was absent, with cerebral tissue floating in amniotic fluid.

**TABLE 2** Results of the analysis of the ultrasound and newborn of the 25 cases analyzed

Case	Ultrasonographic examination	Newborn follow-up
1	Without alterations	Live/cataract
2	Decrease AF, growth restriction	Live
3	Hydrocephaly	Live/speech impairments
4	Insufficient tricuspid	Live
5	Decrease AF, hepatomegaly	Live
6	Without alterations	Live
7	Cranial cap absent	Miscarriage
8	Growth restriction	Fetal death
9	Without alterations	Live/bilateral deep deafness
10	Hydrocephaly, growth restriction, ventricular septal defect	Fetal death
11	Without alterations	Live/ventricular septal defect
12	Growth restriction	Fetal death
13	Atrial septal defect, aortic stenosis	Live/arthritis 6 months
14	Fetal death	Fetal death
15	Hepatomegaly, hydrocephaly, intracranial calcifications	Fetal death
16	Without alterations	Live
17	Without alterations	Live
18	Oligohydramnios, arterial canal patency, aortic stenosis	Live
19	Without alterations	Live
20	Without alterations	Miscarriage
21	Ventricular septal defect	Fetal death
22	Without alterations	Live
23	Without alterations	Live
24	Growth restriction	Fetal death
25	Hydrocephaly, growth restriction, ventricular septal defect	Fetal death

In case n° 25, fetus showed ultrasound abnormalities: echogenic fetal bowel, growth retardation, oligohydramnios, placentomegaly, pericardial effusion, cardiomegaly, hepatomegaly, and ascites. Fetal death occurred at the 29<sup>th</sup> week of gestation. Rubella virus was amplified from placenta and histological diagnosis of the placenta showed active chronic villitis and chorioamnionitis, villous fibrosis, focal calcifications, and thrombotic vasculopathy with avascular villi and hemorrhagic endovasculitis.

#### Newborn follow-up

In the total group of live newborn, 10 newborns did not show change in the ultrasound during the prenatal, but after birth, one newborn showed bilateral deep deafness and other ventricular septal defects. There were 6 cases in which virological analyses of the amniotic fluid samples were positive while the newborn showed no signs of congenital rubella syndrome (cases 6, 16, 17, 19, 22 and 23). These results indicate that not all infected babies developed the congenital disorder. Out of 15 live newborn

with alterations in ultrasound, 4 lived without sequela, and 3 presented alterations after birth: speech impairments and arthritis (Table 2).

#### DISCUSSION

Historically, rubella and congenital rubella syndrome have been an important public health challenge in Brazil. Despite the fact that rubella vaccination was initiated in 1992, regular outbreaks of the disease have been reported since the beginning of 1995 and have continued until 2007.<sup>12,13</sup> Between 1999 and 2008, a large number of rubella cases were reported throughout the country, with the highest incidence among adults and a steady increase in the number of CRI and CRS cases.<sup>11,14</sup> The impact of CRS in life and in the economy of the country was high; therefore, it became necessary to accelerate control and, ultimately, eliminate rubella virus transmission. CRI cases may play an important role as virus-shedders and in the continuation of rubella transmission within the community. Therefore, identifying them to prevent fur-

ther rubella transmission is also important in the context of rubella elimination.<sup>15</sup>

The clinical diagnosis of acute rubella infection in pregnancy is extremely difficult. The rash is not very specific or particularly apparent, and most infectious cases are subclinical.<sup>2,3</sup> Therefore, demonstration of seroconversion and presence of high IgM titers is the primary mode of diagnosis of acute rubella in pregnancy. Unfortunately, booking serum samples are often not available. The risk of congenital infection may usually be estimated by establishing the gestational age at the time of maternal infection. However, diagnosis of intrauterine infection is difficult because often maternal serology is inconclusive especially when infection occurs between the 13<sup>th</sup> and 20<sup>th</sup> weeks of gestation.<sup>2</sup> Direct methods of diagnosing fetal infection by PCR are therefore essential for early diagnosis as shown by another report.<sup>1</sup> Our results showed that all pregnant women studied had positive serology results for IgG and IgM to rubella virus in the first or second sample. In the present cases, prenatal diagnosis was performed after 21 weeks of gestation and the time elapsed between the onset of maternal infection and the procedure was longer than 6 weeks, reducing false-negative results.

The humoral immune response of infants with CRS differs from that of naturally infected or immunized children.<sup>2</sup> Laboratory confirmation is based on the detection of rubella specific IgM and IgG antibodies and low avidity antibody. Fetal blood is not taken for this purpose until about 22 weeks of gestation, when fetal IgM becomes detectable; however, virus-specific IgM levels may be low at this time and therefore false-negative results may be obtained. Rubella is slower than in postnatal infection and low avidity can be detected for a longer period.<sup>2,3,16</sup> The present study confirms the above findings by means of IgM negative in the sera of the four newborns infected. However, these newborns that had no detectable IgM were positive for RV RNA by PCR assays. Among these cases, one newborn showed alterations by ultrasound, arterial canal patency and aortic stenosis another miscarriage. It has also been reported that false-positive IgM results can be obtained with sera from patients with other acute viral infection, such as measles, parvovirus B19, cytomegalovirus and Epstein-Barr virus infection.<sup>17</sup> Our finding that one newborn with rubella IgM reactivity was diagnosed with cytomegalovirus infection supports this observation. It becomes evident that unspecific stimulation of immune cells or cross-reacting antibodies can also be found in the fetal system.

Concerning the PCR results, rubella was detected in all amniotic fluid samples of mothers of infected fetuses.

Macé et al.<sup>5</sup> report involving 45 pregnant mothers of rubella-infected fetuses, (83%) were rubella-positive. Furthermore, results similar to these were reported by Bosma et al.<sup>4</sup> and Jin et al.<sup>18</sup> PCR is a rapid and sensitive molecular method and it has not been applied systematically to CRS cases. It can be used in conjunction with serology for the diagnosis of acute infection and also for the diagnosis of pre and post-natal CRS since the serological results can be inconclusive.<sup>3,4,5,19</sup> However, detection of rubella viral RNA in AF which may be obtained from amniocentesis at about 12 weeks of gestation allows confirmation of fetal infection. The time between maternal infection and fetal sampling is an important consideration in prenatal diagnosis. The optimal sampling interval between maternal infection and fetal sampling should be 6 to 8 weeks for amniotic fluid and fetal blood.<sup>5</sup>

The consequences of rubella during pregnancy may be the birth of a child with congenital anomalies, which may be severe, and multiple birth of a child apparently normal or spontaneous abortion.<sup>20</sup> Rubella virus generally establishes a chronic nonlytic infection in the fetus and has the potential to infect any organs.<sup>21,22</sup> The rubella virus teratogenic process most probably begins when placental infection occurs during maternal viremia, leading to dissemination of the virus throughout the fetus. In addition, tissues from different organs of fetuses with CRS revealed teratogenic effects, such as reduced cell size and number compared with control, which was suggestive of mitotic inhibition or perhaps due to rubella induced chromosomal breaks.<sup>21</sup> Even when the fetus is infected, it survives in most cases; the pregnancy continues and premature births or stillbirths can occur.<sup>3</sup> In our results, the most common ultrasonographic prenatal rubella infection findings were heart and amniotic fluid anomalies. Hydrocephaly, although rare in congenital rubella, was observed in three cases. Absence of the skullcap with cerebral tissue floating in the amniotic fluid was diagnosed in case n° 7 and the virus was detected in the placenta, liver, and central nervous system. Miller et al.<sup>9</sup> also report two fetuses with the same alterations. A ventricular septal defect was observed in two cases and an atrial septal defect associated with aortic stenosis was diagnosed in one case. Case n° 25 also showed several changes in placenta due to viral replication. As a result of prenatal diagnosis, it is clear that not all infected fetuses developed CRS. The simplest hypothesis implies that the decisive parameter is the replication level of the virus in the fetus, i.e. when virus replication in the fetus surpasses a certain critical level, the fetus would then develop CRS. If this does not occur, the fetus would remain undisturbed. It is noteworthy that rubella genome was de-

tected in the amniotic fluid, POC and placenta due to the infection of the mothers and also from a newborn that died with severe congenital disorders. In addition, antibodies IgG against rubella virus were transmitted from the mother to the fetus, while IgM antibodies were not transmitted but produced in the fetus from around 20 weeks of gestation. However, these antibodies could not eliminate the virus from the fetal body although they had neutralizing activity. Elimination of the virus from the infected tissue is dependent on cell-mediated immunity. At around 1 year of age, its ability becomes completely mature and thus the body is able to eliminate the virus. In contrast, in the case of infected eye lens, the virus cannot be completely eliminated from the lens. Once the virus enters the lens, it replicates and persists without elimination.<sup>3</sup>

In Brazil there are not many reports about CRI, because the diagnosis of infection with rubella virus during pregnancy or congenital rubella syndrome is performed only after the birth of the child. In some countries, the risk of disease in the first trimester justifies termination of pregnancy without prenatal diagnosis, which is not allowed in Brazil, because Brazilian law does not allow therapeutic abortion.

## RESUMO

Diagnóstico pré-natal de infecção congênita por rubéola, em São Paulo, Brasil.

**Objetivo:** a rubéola, durante os primeiros estágios da gravidez, pode levar a graves defeitos congênitos, conhecidos como síndrome da rubéola congênita (SRC). Amostas de gestantes com sintomas e suspeitas da rubéola congênita foram coletadas entre 1996 e 2008.

**Métodos:** um total de 23 amostras de fluido amniótico, 16 amostras de sangue fetal, um produto da concepção e uma placenta foram analisados por sorologia e PCR.

**Resultados:** todas as gestantes apresentaram sorologia positiva para IgG/IgM para o vírus da rubéola. Entre os recém-nascidos, 14 apresentaram anticorpos IgG positivos e 11 foram os anticorpos IgM positivos. Das 25 amostras analisadas neste estudo, 24 eram positivas por RT-PCR. Alterações na ultrassonografia foram encontradas em 15 (60%) dos 25 fetos infectados com o vírus da rubéola. Morte fetal e aborto espontâneo foram reportados em 10 (40%) dos 25 casos analisados. O vírus da rubéola foi amplificado por PCR em todos os fetos que apresentaram alterações na ultrassonografia, compatíveis com a

rubéola. Morte fetal e aborto foram relatados em 10 dos 25 casos analisados.

**Conclusão:** os resultados mostraram que os ensaios moleculares são ferramentas importantes para o diagnóstico precoce da rubéola e da síndrome da rubéola congênita.

**Palavras-chave:** ultrassonografia pré-natal; síndrome da rubéola congênita; líquido amniótico; diagnóstico, RT-PCR; sorologia.

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# Dietary patterns are associated with general and central obesity in elderly living in a Brazilian city

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## SUMMARY

**Objective:** dietary pattern evaluation is often used in order to determine whether a diet is healthy, as well as to predict the onset of diseases. This study aimed to identify dietary patterns, and to examine their associations with general (body mass index) and central (waist circumference and waist-to-hip ratio) obesity in community-living elderly in a Brazilian city.

**Methods:** this cross-sectional study included 126 elderly subjects aged 60 or older (57.1% females and mean age  $74.2 \pm 6.46$  years). Anthropometric variables, weight, height, waist (WC) and hip (HC) circumferences, were measured. Body mass index (BMI) and waist-to-hip ratio (WHR) were calculated. Answers to a Food Frequency Questionnaire were interpreted by Principal Component Analysis in order to identify dietary patterns.

**Results:** five dietary patterns were identified and named as prudent (fruit, vegetables and meat), sweets and fats (pastries, sugary foods, fatty foods, whole milk), typical Brazilian (fried eggs, cooked beans, beef, candy, string beans, fried cassava), Mediterranean (fruit, vegetables, olive oil and nuts) and traditional meal (rice and beans). Moderate and high adherences to the Mediterranean pattern were protective factors to general and central obesity (WHR). High adherence to prudent was also protective to central obesity (WC).

**Conclusion:** adherences to the dietary patterns prudent and Mediterranean were protective factors to general and central obesity in elderly.

**Keywords:** elderly, dietary pattern, obesity, anthropometry, cross-sectional studies.

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## INTRODUCTION

The elderly population in Brazil has increased rapidly,<sup>1</sup> and by 2025, will rank sixth largest in the world.<sup>2</sup> The number of elders, in relation to the total Brazilian population, grew from 7.3% in 1991, to 8.56% in 2000<sup>3</sup> and to 10.8% in 2010.<sup>4</sup> Mortality and birth rate reductions correspond to factors associated with the elderly population rising.<sup>5</sup> The World Health Organization considers ages 60+ or 65+ years when referring to the older population in developing and developed countries, respectively.

Diet is a changeable factor that can help healthy aging. The analysis of nutrient intake does not result in a clear understanding of its quality. Since a daily diet con-

sists of a diversity of foods and a large concentration of nutrients, the analysis of dietary patterns becomes the best alternative to evaluating healthy behaviors.<sup>6,7</sup>

Diet and nutrition have been studied as factors for promoting and maintaining health throughout life.<sup>8</sup> Dietary patterns have been associated with non-communicable chronic diseases,<sup>9-13</sup> mortality,<sup>14-16</sup> cognitive function,<sup>17</sup> obesity<sup>10,12,18-19</sup> and the protective effect on being overweight.<sup>14,18,20-21</sup>

Unhealthy dietary patterns (sugar, fat, processed foods and refined grains) can be found in overweight younger adults<sup>20,22</sup> as well as in the elderly.<sup>10,19</sup> Moreover, such patterns can be related to measurements above the recom-

mended waist circumference and waist-to-hip ratio in adults and the elderly.<sup>12,23</sup> Several studies have shown that healthy food (fruit, vegetable, low fat meat and fiber rich products) may promote a protective effect against general [body mass index, (BMI)]<sup>18,20,24</sup> and central [waist-to-hip ratio (WHR) and waist circumference (WC)] obesity.<sup>14,18,21,24</sup>

Although it seems obvious that unhealthy dietary patterns may be associated with obesity, this issue may be debatable. In fact, other studies have identified no positive relationship between obesity and unhealthy dietary patterns in both elderly<sup>14</sup> and younger adults.<sup>25</sup> Examining children and adults, previous study showed the association between healthy food intake (fruit and vegetables) and obesity reduction (adiposity/overweight) is not clear.<sup>26</sup> Thus, the current study attempts to characterize the dietary patterns, and verify their association with health-related variables in the elderly population of a Brazilian city.

## METHODS

### Subjects

The study was conducted in Botucatu, which is a city with 130,201 inhabitants<sup>27</sup> and is located (22°53'09" south latitude, 48°26'42" west longitude) in the state of Sao Paulo, Brazil. Data were collected at the participants' houses from May to November 2008. The sample consisted of 126 individuals older than  $\geq 60$  years. Inclusion criteria were pre-defined as follows: residing in a community (city of Botucatu, SP, Brazil),<sup>3</sup> 60 years and agreeing to participate in the study. The sample (base sample) was sourced from a database obtained in a previous study conducted in Botucatu City.<sup>28</sup> From the base sample of 365 elderly, 185 subjects were randomly selected to be part of a database of the current study. The initial contact was made by telephone, followed by a household interview, anthropometric measurements and a dietary record. Fifty-nine subjects were excluded due to several reasons (refusal to participate in the study, 34; unanswered phone, 13; death, 3; use of vitamins, 3; absence of records of their primary health, 3; hospitalization, 2; absence, 1), with 126 subjects remaining. All procedures were in accordance with the Helsinki Declaration for human rights, and the study was approved by the Research Ethics Committee of the Botucatu School of Medicine (UNESP). All patients or their legal guardians signed a Free-Consent form.

### Anthropometric measures

Weight and height were measured according to Lohman (1988).<sup>29</sup> Subjects were weighted dressed in light clothing and barefoot in a digital scale (Toledo®), with 150 kg ca-

capacity and 0.1 kg accuracy. Height was recorded using a portable stadiometer (Sanny®) with the subjects standing erect without shoes and with the feet together. For bedridden elderly persons, the weight and height were estimated by the Chumlea formula.<sup>30-31</sup>

Body mass index (BMI) was calculated by dividing the weight by height squared (kilograms/meters<sup>2</sup>) of the subjects. The classification of nutrition status by BMI was performed according to cutoff points established by the Pan American Health Organization<sup>32</sup> [low weight ( $\leq 23$  kg/m<sup>2</sup>), normal weight for height ( $23 < \text{BMI} < 28$  kg/m<sup>2</sup>) and overweight ( $\geq 28$  kg/m<sup>2</sup> overweight and obese  $\geq 30$  kg/m<sup>2</sup>)].

Waist (WC) and hip (HC) circumferences were measured using a non-elastic tape. WC was measured with the subject standing up, at the end of normal expiration, by using the tape at a point midway between the inferior margin of the lowest rib and the iliac crest, whereas HC was recorded at maximum posterior extension of the hip<sup>29</sup>. The waist-to-hip ratio (WHR) was calculated by dividing WC by HC. Waist circumference was considered high when its values were above 88 cm for women and 102 cm for men.<sup>33</sup> WHR was considered elevated when its values were above 0.85 for women and 1 for men.<sup>33</sup> All measurements were performed by the same investigator (1<sup>st</sup> author of this study), with the same tape, stadiometer and scale.

### Dietary intakes

The evaluation of the estimated daily intake was performed by using a food frequency questionnaire (FFQ)<sup>34</sup> with adaptation (inclusion of cooked sweet potatoes, chicory, pepper, lime, mango, beets, green beans, poached eggs and nuts). Besides daily intake, the FFQ was used to evaluate the individuals' frequency of consumption (from 0-10 times a day, week, month or year).<sup>35</sup>

### Statistical analysis

The dietary intake information obtained by FFQ was analyzed and interpreted for identification of the dietary patterns by exploratory factor analysis (Principal Component Analysis, PCA). In this method, data are summarized, and correlated variables are grouped.

Some food items were excluded from the analysis because they displayed low intake frequency. One hundred and twenty-one food items were included in the PCA.

Kaiser-Mayer-Olkin (KMO) measurement and Bartlett's Test of Sphericity (BTS) were applied to evaluate PCA applicability. In order to obtain the dietary patterns, varimax rotation was used, and based on the correlation

matrix. The number of factors was determined by taking into account loading values greater than or equal to 0.3, and the percentage of explained variation. Food items with negative loadings were excluded from each pattern.

Cronbach's  $\alpha$  coefficient was obtained for each factor by evaluating the consistency and the characteristics of each food and the effect of its exclusion on the final coefficient value.

The scores of individual intake were obtained from the dietary patterns and categorized into tertiles, i.e. the 1<sup>st</sup> as low, the 2<sup>nd</sup> as moderate and 3<sup>rd</sup> as high adherence to the pattern.

The variables BMI [(presence (BMI  $\geq$  28 kg/m<sup>2</sup>) or absence (BMI  $\leq$  28 kg/m<sup>2</sup>) of overweight] and WC [presence ( $\geq$  88cm, women;  $\geq$  102cm, men) or absence ( $<$ 88cm, women;  $<$ 102cm, men) of increased values] were categorized dichotomously. For the waist-hip ratio, the elevated values were considered when they were above 0.85 for women and 1 for men.

Logistic regression models were fitted by considering general or central obesity as an outcome and the variables of interest (low, moderate and high adherence to dietary patterns) as an explanatory control for age and sex.

All analyses were performed by software SAS (Statistical Analysis System, Cary, North Carolina) and SPSS (Statistical Package for Social Sciences, Armonk, New York) for Windows, versions 9.2 and 19.0, respectively.

## RESULTS

One hundred and twenty-six elderly individuals were evaluated. Of these, 72 (57.1%) were females aged 65 to 95 years ( $74.2 \pm 6.46$ ). By using the Kaiser-Mayer-Olkin (KMO) coefficient and the Barlett Test of Sphericity (BTS), appropriate conditions were verified for application of Principal Component Analysis (PCA) and patterns (factors) were extracted. By factor analysis, it was possible to identify 5 dietary patterns in this population, which explained 21.11% of the total variance of food intake. In our study, the pattern labeled as prudent presented the highest variance percentage (5.64%), followed by sweets and fats (4.48%), typical Brazilian pattern (4.05%), Mediterranean (3.72%) and traditional meal (3.22%).

Table 1 shows the anthropometric characteristics of 126 elderly. Table 2 shows the factor loading (obtained after varimax rotation) of each food item composing the dietary factor (pattern) found. The items with factor loading higher than 0.3 were maintained in order to compose the dietary pattern. Cronbach's  $\alpha$  coefficient was analyzed for each factor (pattern). Variability of food intake by in-

dividual in that pattern was considered high when the Cronbach's  $\alpha$  coefficient value was higher than 0.6. On the other hand, variability was considered low when that coefficient values was lower than 0.6.

**TABLE 1** Anthropometric characteristics of participants

	All	Men	Women
Number of subjects <sup>2</sup>	126	54	72
Age (y) <sup>1</sup>	74.1 (6.6)	73.4 (6.3)	74.7 (6.8)
BMI (kg/m <sup>2</sup> ) <sup>1</sup>	27.2 (4.7)	26.3 (4.2)	28 (5)
Overweight (BMI 28 – 30 kg/m <sup>2</sup> ) <sup>2</sup>	20 (15.9)	8 (14.8)	12 (16.7)
Obese (BMI $\geq$ 30 kg/m <sup>2</sup> ) <sup>2</sup>	29 (23)	9 (16.7)	20 (27.8)
WC (cm) <sup>1</sup>	94 (12.4)	97.4 (11.4)	91.5 (12.6)
HC (cm) <sup>1</sup>	104.8 (10.6)	101.1 (6.7)	107.6 (11.9)
WHR1	0.9 (0.09)	0.96 (0.08)	0.85 (0.06)

BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio.  
<sup>1</sup> data are mean ( $\pm$  standard deviation).

<sup>2</sup> data are number (%).

**TABLE 2** Foods and factor loading for the five dietary patterns identified

Foods	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
Cooked rice	- 0.206	0.142	0.287	- 0.029	0.367
Sweet biscuits	0.134	0.385	0.082	- 0.135	0.113
French fries	- 0.055	0.323	0.223	- 0.180	- 0.066
Boiled potato	0.424	- 0.113	0.116	0.060	0.163
Boiled cassava	0.488	- 0.166	0.193	- 0.443	- 0.098
Fried cassava	0.148	0.127	0.329	- 0.245	- 0.067
Baked sweet potatoes	- 0.010	0.400	0.040	- 0.011	0.135
Sugar	- 0.180	0.420	0.214	- 0.278	0.165
Ice cream	0.051	0.337	0.126	0.175	0.025
Cooked beans	- 0.350	0.025	0.384	0.028	0.330
Chard	0.372	- 0.217	0.201	0.448	0.204
Watercress	0.423	0.161	- 0.031	0.049	0.035
Chicory	0.458	- 0.106	0.137	- 0.338	0.057
Escarole	0.425	- 0.274	0.104	- 0.262	0.174
Broccoli	0.706	- 0.299	0.247	0.152	0.025
Cauliflower	0.506	- 0.036	0.216	0.356	0.085
Spinach	0.415	0.218	- 0.225	- 0.020	0.142
Courgette	0.663	- 0.199	0.074	- 0.303	0.108
Eggplant	0.695	- 0.228	- 0.030	- 0.121	- 0.081
Chayote	0.556	- 0.184	0.274	- 0.201	- 0.074
Pepper	0.230	0.002	0.296	0.335	0.105
Tomatoes	0.315	0.171	0.136	0.328	0.030
String beans	0.609	- 0.233	0.335	- 0.050	0.109

(continue)

**TABLE 2** Foods and factor loading for the five dietary patterns identified (continuation)

Foods	Pattern 1	Pattern 2	Pattern 3	Pattern 4	Pattern 5
Beets	0.491	- 0.320	0.284	0.139	- 0.178
Carrots	0.545	- 0.039	0.107	0.124	0.047
Pineapple	0.517	- 0.098	0.098	- 0.329	- 0.045
Avocado	0.197	- 0.002	0.042	0.366	0.124
Banana	0.050	0.064	0.241	0.374	- 0.133
Guava	0.308	0.314	- 0.288	0.050	- 0.006
Orange	0.307	0.036	0.165	0.252	0.020
Lime	0.102	0.313	0.120	0.242	0.250
Apple	0.319	0.020	0.125	- 0.094	- 0.033
Papaya	0.437	- 0.044	0.140	0.134	0.030
Mango	0.378	0.040	- 0.046	- 0.271	- 0.507
Watermelon	0.537	- 0.088	0.102	- 0.394	- 0.122
Strawberry	0.466	- 0.038	0.181	- 0.199	- 0.174
Peach	0.353	0.234	- 0.106	0.107	- 0.423
Whole milk	- 0.035	0.355	0.168	- 0.098	0.147
Prato cheese	0.086	0.151	0.093	0.328	- 0.375
Parmesan cheese	0.300	0.153	- 0.280	0.375	- 0.009
Mozzarella cheese	0.106	0.235	0.125	0.388	- 0.289
Milk cream	0.240	0.317	- 0.092	- 0.031	- 0.166
Olive oil	0.287	0.064	0.014	0.443	- 0.032
Fried eggs	- 0.141	0.189	0.422	- 0.090	- 0.045
Boiled eggs	0.051	0.303	0.150	- 0.035	0.103
Poached eggs	0.228	0.362	- 0.177	- 0.106	0.067
Fish	0.421	0.036	- 0.283	0.171	0.268
Salt cake	0.215	0.442	- 0.206	- 0.196	0.005
Pizza	0.147	0.533	0.126	0.153	- 0.112
Beef	0.152	- 0.187	0.359	0.020	0.096
Pork	- 0.066	0.367	0.173	- 0.244	- 0.087
Poultry	0.306	- 0.159	- 0.082	- 0.201	0.209
Homemade sweets	0.143	0.537	- 0.120	0.071	- 0.024
Industrialized sweets	- 0.072	0.325	0.293	- 0.236	0.120
Sweet milk	- 0.034	0.416	0.182	0.017	0.036
Candy	- 0.093	0.298	0.358	- 0.046	0.151
Sweets in syrup	0.248	0.490	- 0.145	- 0.122	- 0.132
Nuts	0.153	- 0.108	- 0.190	0.320	0.003
Cronbach's $\alpha$	0.768	0.518	0.348	0.57	0.821

Table 3 shows the five patterns identified. Dietary pattern 1 was mainly loaded with fruit, vegetables and low fat meat and was labeled as prudent. Pattern 2 was mainly rich in foods with high energy, such as, sweets, pork, and french fries and was named the sweets and fats. Pattern 3 contained legumes, meat, vegetables, fried eggs and fried carbohydrates (cassava, in this case), which are foods usually

used in the preparation of Brazilian people's meals, and was called the typical Brazilian pattern. Pattern 4 was rich in fruits, vegetables, monounsaturated fats (olive oil, avocado and nuts), low amounts of foods from animal sources, and was designated the Mediterranean. Pattern 5 contained cooked rice and beans, which represented the basis of Brazilian meals, and was labeled the traditional meal.

**TABLE 3** Food items of the five factors identified

Dietary pattern	Foods
Dietary pattern 1 Prudent Variance explained: 5.64%	Broccoli, eggplant, courgette, string beans, chayote, carrots, watermelon, pineapple, cauliflower, beets, boiled cassava, strawberry, chicory, papaya, escarole, boiled potato, watercress, fish, spinach, mango, chard, peach, apple, orange, poultry
Dietary pattern 2 Sweets and fats Variance explained: 4.48%	Homemade sweets, pizza, sweets in syrup, salt cake, sugar, sweet milk, baked sweet potatoes, sweet biscuits, pork, whole milk, ice cream, industrialized sweets, french fries, milk cream, guava, lime, poached eggs, boiled eggs
Dietary pattern 3 Typical Brazilian pattern Variance Explained: 4.05%	Fried eggs, cooked beans, beef, candy, string beans, fried cassava
Dietary pattern 4 Mediterranean Variance explained: 3.72%	Chard, olive oil, mozzarella cheese, parmesan cheese, banana, avocado, cauliflower, pepper, tomatoes, prato cheese, nuts
Dietary pattern 5 Traditional meal Variance explained: 3.22%	Cooked rice, cooked beans

Associations between dietary pattern adherence *versus* general and central obesity are showed in Table 4. The adherence to Mediterranean and prudent patterns were protective factors for obesity. In detail, moderated adherence to Mediterranean was a protective factor to general obesity (values above the recommended BMI) (OR 0.243, 95% CI 0.093-0.635). High adherence to the same pattern was a protective factor to central obesity (values above the recommended for WHR) (OR 0.027, 95% CI 0.109-0.706). High adherence to prudent was a protective factor for central obesity (values above the recommended WC) (OR 0.160, 95% CI 0.031-0.835).

**TABLE 4** Dietary patterns and overweight (BMI), WHR and WC association in 126 elderly

Variables	Adherence to patterns	BMI		WHR		WC	
		p-value	OR (95% CI)	p-value	OR (95% CI)	p-value	OR (95% CI)
Pattern 1 Prudent	High	0.22	0.626 (0.250-1.567)	0.36	1.015 (0.402-2.561)	0.01	0.160 (0.031-0.835)
	Moderate	0.47	1.051 (0.433-2.554)	0.05	2.158 (0.870-5.356)	0.03	1.390 (0.455-4.241)
	Low	–	1.0	–	1.0	–	1.0
Pattern 2 Sweets and fats	High	0.77	0.679 (0.265-1.735)	0.28	0.595 (0.227-1.557)	0.09	0.249 (0.061-1.025)
	Moderate	0.39	0.585 (0.233-1.473)	0.76	0.869 (0.348-2.172)	0.75	0.596 (0.190-1.872)
	Low	–	1.0	–	1.0	–	1.0
Pattern 3 Typical Brazilian	High	0.57	0.497 (0.202-1.226)	0.77	1.026 (0.414-2.544)	0.20	1.451 (0.429-4.907)
	Moderate	0.15	0.386 (0.151-0.991)	0.51	1.318 (0.522-3.328)	0.18	0.558 (0.145-2.153)
	Low	–	1.0	–	1.0	–	1.0
Pattern 4 Mediterranean	High	0.33	0.332 (0.133-0.830)	0.02	0.027 (0.109-0.706)	0.29	0.357 (0.104-1.222)
	Moderate	0.04	0.243 (0.093-0.635)	0.94	0.513 (0.207-1.269)	0.48	0.402 (0.114-1.419)
	Low	–	1.0	–	1.0	–	1.0
Pattern 5 Traditional meal	High	0.94	0.860 (0.346-2.139)	0.10	0.586 (0.229-1.494)	0.98	0.995 (0.297-3.341)
	Moderate	0.68	0.785 (0.313-1.969)	0.18	1.316 (0.530-3.269)	0.98	1.009 (0.300-3.391)
	Low	–	1.0	–	1.0	–	1.0

BMI, body mass index; WHR, waist to hip ratio; WC, waist circumference. Odds ratio adjusted for age and sex.

## DISCUSSION

The current study conducted in community-living elderly identified five dietary patterns named as prudent, sweets and fats, typical Brazilian pattern, Mediterranean and traditional meal. Our results showed that moderate and high adherences to the Mediterranean pattern are protective factors to general (BMI) and central obesity (WHR), respectively; whereas high adherence to prudent may have a beneficial effect on central obesity (WC). To our knowledge, this is the first time that dietary patterns and their effects on general and central obesity in Brazilian elderly have been evaluated.

The 5 patterns found represented 21.11% of the total variance. This value was similar (21%) to that found in a previous study conducted on Italians elderly, which identified 4 dietary patterns.<sup>10</sup> The FFQ currently applied<sup>34</sup> has been used in previous studies.<sup>36-38</sup> The good reproducibility for associations currently observed by applying FFQ and PCA was also identified by another author.<sup>39</sup> In fact, FFQ can be applied in epidemiological studies, since it is able to associate the frequency of intake of certain dietary factors with variables of interest.<sup>34,40</sup>

The named Mediterranean pattern included health foods from a plant source, olive oil, avocados and nuts, although also comprised some kind of cheeses with high fat amount (mozzarella, parmesan and prato cheese). Since it contains foods that are rich in monounsaturat-

ed fatty acids, it is considered to be a cardioprotective diet.<sup>16,41-42</sup> The inverse association between adherence to the Mediterranean diet and cardiovascular disease has been shown in a study that examined event occurrences (myocardial infarction, stroke, or death from cardiovascular causes) in the 4.8 years of follow-up in a population aged 55-80 years,<sup>43</sup> and by meta-analysis that evaluated mortality risk.<sup>44</sup> This diet pattern also has been associated with lower general mortality in Europe.<sup>16,45-46</sup>

Our results showed that moderate and high adherences to Mediterranean pattern are protective factors to general (BMI) and central obesity (WHR), respectively. Previous study identified the Mediterranean pattern and WHR as factors independently associated with the ischemic stroke occurrence in elderly and other adults.<sup>47</sup> Spanish researchers found an inverse association between obesity (BMI and WC) and a healthy life style, including adherence to the Mediterranean diet<sup>48</sup> by the elderly. Examining adults, prospective studies also have shown that adherence to the Mediterranean diet was negatively associated with WC<sup>49</sup> and with weight gain ( $\geq 5$  kg).<sup>50</sup> On the other hand, some studies found no protective effect of the Mediterranean diet on weight gain in adults and elderly.<sup>51-53</sup>

Also found in other studies,<sup>8,14,21</sup> the prudent dietary pattern has been associated with the reduction of all-cause mortality<sup>54</sup> and hypertension.<sup>12,55</sup> In the current study,

high adherence to this dietary pattern was a protective factor for central obesity (WC). Similar results were identified in the elderly<sup>56-58</sup> and adults.<sup>56,59-60</sup>

The sweets and fats pattern has been found in several researches.<sup>8,16,61</sup> It represents a concerning dietary pattern since it contains foods that are associated with the high prevalence of chronic diseases.<sup>8</sup> In fact, elderly people tend to show a high percentage of non-communicable chronic diseases, such as hypertension, cardiovascular diseases and diabetes.<sup>62-64</sup> However, it is important to note that other factors are associated with chronic diseases, such as genetic ones. Absence of the association between obesity and this dietary pattern was currently found. Conversely, the dietary pattern containing sweets and fats was associated with a high BMI in the elderly and adults,<sup>59,61,65</sup> elevated WC in adults<sup>59,61</sup> and high mortality in elderly men.<sup>16</sup>

Another dietary pattern, typical Brazilian, represents the standard Brazilian meal which contains a type of meat, a legume (beans, in this case), a fried carbohydrate (cassava), a vegetable, and fried eggs. Examining results from the Family Budget Study (children, adults and elderly individuals), a study found that the typical Brazilian pattern contains foods that were noteworthy in the dietary representation from all Brazilian regions.<sup>66</sup> The absence of the association with this dietary pattern and obesity was evident in our study. To the best of our knowledge, no studies have addressed this issue. Therefore, comparisons cannot be made.

The traditional meal pattern is incorporated into the population's habits from the North to the South of Brazil and in all age ranges.<sup>66</sup> The comparison of this pattern with international studies is not actually feasible since this combination of rice and beans is typically Brazilian. We did not identify the association of this dietary pattern with obesity in the elderly. Some national studies performed in adult populations showed that this pattern was inversely associated with WC<sup>61</sup> and was associated with lower risk factors for weight gain.<sup>61,67-68</sup>

It is important to emphasize that the metabolic syndrome is a frequent condition among elderly<sup>69-71</sup> and that central obesity is a risk factor for this disorder.<sup>72</sup> In the present study, we showed central obesity may have been protected by high adherence to the Mediterranean and prudent patterns, and general obesity may have been protected by moderated adherence to the Mediterranean dietary pattern. Recent systematic review identified evidences of adherence to the Mediterranean diet and protective effects in adults and elderly subjects with metabolic syndrome.<sup>73</sup> Thus, the adherence to those dietary patterns

may contribute to diminishing the metabolic syndrome prevalence.

It is worth mentioning that the current population cannot be considered representative of the whole Brazilian community-living elderly, since they came from a Brazilian small city. Other limiting factors should also be mentioned, such as the sample size, study design (cross-sectional) and method for identifying the dietary patterns, which is not defined as a gold standard.

Although longitudinal studies with larger numbers of elderly are needed, health programs, including the formulation of policies for dietary education and health care, should be adopted to prevent obesity in older people.

## CONCLUSION

In summary, our study identified that moderate and high adherences to the Mediterranean pattern are protective factors to general (BMI) and central obesity (WHR), whereas high adherence to the prudent pattern is a protective factor to central obesity (WC) in the elderly.

In spite of the limitations discussed, the outcomes of this study contribute to the literature by furthering the knowledge of the relationship between dietary patterns and obesity in the elderly. Longitudinal studies using a larger sample size are needed to test the hypothesis of the possible obesity protecting effect of the Mediterranean and prudent dietary patterns on community-living elders.

## AUTHOR'S CONTRIBUTIONS

PLM performed the data collection. JEC and PLM worked on data analysis and interpretation, and statistical analysis. PJFVB, PLM, JEC and ALAF wrote the final version of the manuscript. All authors evaluated the results, contributed with their comments, and approved the final version of the manuscript before submission for publication.

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## RESUMO

Padrões alimentares associados com obesidade geral e central em idosos residentes em uma cidade brasileira.

**Objetivo:** a avaliação do padrão alimentar é muitas vezes usada para determinar se uma dieta é saudável, bem como para prever o aparecimento de doenças. Este estudo teve como objetivo identificar padrões alimentares e analisar as suas associações com obesidade geral (índice de massa corporal) e central (circunferência da cintura e relação cintura-quadril) em idosos residentes em comunidade em uma cidade brasileira.

**Métodos:** este estudo transversal incluiu 126 idosos com 60 anos ou mais de idade (57,1% do sexo feminino e média de idade  $74,2 \pm 6,46$  anos). As variáveis antropométricas [peso, altura, circunferências da cintura (CC) e do quadril (CQ)] foram mensuradas. Foram calculados o índice de massa corporal (IMC) e relação cintura-quadril (RCQ). As respostas a um questionário de frequência alimentar foram interpretadas por Análise de Componentes Principais, a fim de identificar os padrões alimentares.

**Resultados:** cinco padrões alimentares foram identificados e nomeados como prudente (frutas, legumes e carne), doces e gorduras (alimentos de pastelaria, doces, alimentos gordurosos, leite integral), padrão tipicamente brasileiro (ovos fritos, feijão cozido, carne, caramelo, vagens, mandioca frita), Mediterrâneo (frutas, legumes, azeite de oliva e nozes) e tradicional (arroz e feijão). Adesões moderada e alta ao padrão Mediterrâneo foram fatores de proteção para obesidade geral e central (RCQ). Alta adesão ao padrão prudente também foi protetor contra a obesidade central (CC).

**Conclusão:** adesões aos padrões alimentares prudente e Mediterrâneo foram fatores de proteção para obesidade geral e central em idosos.

**Palavras-chave:** idoso, padrão alimentar, obesidade, antropometria, estudos transversais.

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# Risk factors for episiotomy: a case-control study

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## SUMMARY

**Objective:** obtaining information on the factors associated with episiotomy will be useful in sensitizing professionals to the need to minimize its incidence. Therefore, the objective of this study was to evaluate risk factors for episiotomy in pregnant women who had undergone vaginal delivery at a university maternity hospital in northeastern Brazil.

**Methods:** a case-control study was conducted with pregnant women submitted to episiotomy (cases) and pregnant women not submitted to episiotomy (controls) between March 2009 and July 2010 at the Professor Fernando Figueira Integral Medicine Institute (IMIP) in Recife, Brazil, in a ratio of 1 case to 2 controls. The study variables consisted of: whether episiotomy was performed, demographic, obstetric and fetal characteristics (primiparity, analgesia, instrumental delivery, fetal distress, etc.), external factors (day and time of delivery, professional attending delivery) and factors directly related to delivery. Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Multivariate analysis was performed to determine the adjusted risk of episiotomy.

**Results:** a total of 522 women (173 cases and 349 controls) were included. It was found that deliveries with episiotomy were more likely to have been attended by staff physicians (OR = 1.88; 95%CI: 1.01 - 3.48), to have required forceps (OR = 12.31; 95%CI: 4.9 - 30.1) and to have occurred in primiparas (OR = 4.24; 95%CI: 2.61 - 6.89). The likelihood of a nurse having attended the delivery with episiotomy was significantly lower (OR = 0.29; 95%CI: 0.16 - 0.55).

**Conclusion:** episiotomy was found to be strongly associated with deliveries attended by staff physicians, with primiparity, and with instrumental delivery, and was less common in deliveries attended by nurses.

**Keywords:** episiotomy, natural childbirth, risk factors, perineum/injuries, case-control studies.

Study conducted at the Professor Fernando Figueira Integral Medicine Institute (IMIP), Recife, PE, Brazil

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## INTRODUCTION

Episiotomy, which consists in an incision on the perineum to widen the birth canal, was for a long time the principal procedure performed during childbirth. With the objective of protecting the pelvic floor and preventing fetal trauma during birth, its routine use was widely accepted in the past, principally in primipara (woman in her first labor and delivery).<sup>1</sup>

Nevertheless, a systematic review available in the Cochrane Library showed that episiotomy is not only a pro-

cedure that should not be performed routinely but also it is both unnecessary and possibly harmful. That Cochrane review included eight randomized clinical trials, involving more than 5,000 women. Routine episiotomy was found to be associated with greater blood loss during childbirth, perineal pain, an increased risk of severe perineal laceration, a greater risk of scarring complications and a greater need for stitches, with no clearly demonstrated benefit to the mother and/or infant. On the contrary, the authors

concluded that the benefits of selective episiotomy (indicated under special circumstances) are much greater than those found with routine episiotomy.<sup>2</sup>

Although the occasions in which a selective episiotomy should be performed are yet to be defined, publication of the results of controlled clinical trials and of the Cochrane systematic review has led to a significant decline in the rates of this procedure.<sup>3,4</sup> Since 1996, the World Health Organization has stipulated an episiotomy rate of around 10% as being acceptable,<sup>5,6</sup> although the procedure continues to be performed routinely by a variety of professionals in various countries.<sup>7</sup>

Evidence suggests a need for continued medical education and programs aimed at sensitizing the professionals involved in attending childbirth in order to reduce the use of this procedure.<sup>3,7,8</sup> There is also a need to document the factors associated with the use of episiotomy and to monitor the progressive reduction in its use following introduction of a policy adopted to restrict its practice.

Therefore, the present study was conducted with the objective of describing the frequency of episiotomy in a university maternity hospital in the Northeast of Brazil and identifying the principal factors associated with the procedure.

## METHODS

An analytical, observational, case-control study was conducted with women who had undergone vaginal delivery at the (IMIP) in Recife, Pernambuco, Brazil. The study was conducted between March 2009 and July 2010 following approval by the institution's internal review board (reference #1284-08). All the women voluntarily agreed to participate in the study and signed an informed consent form.

Sample size was calculated using the Statcalc module of the Epi-Info program, version 3.5.3. (Atlanta, GA, USA). Considering a frequency of forceps delivery without episiotomy of 1% and an odds ratio (OR) of 7.0<sup>9</sup> for a case to control ratio of 1:2, 173 cases and 349 controls would be required to show a difference, making a total of 522 women.

A consecutive convenience sample was obtained, consisting of all the women who fulfilled the eligibility criteria and who were in the maternity ward when the investigators made their visits every other day, during the day shift. The women were interviewed immediately following delivery, prior to their release from hospital. The inclusion criterion was having had an assisted vaginal de-

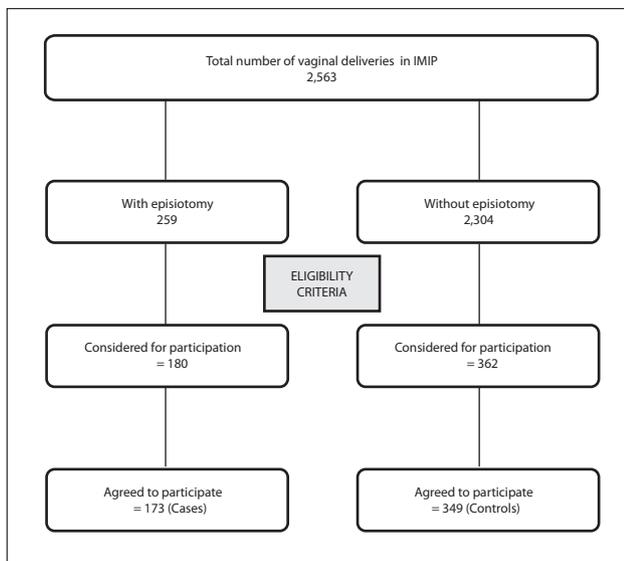
livery at IMIP. Women who had been submitted to episiotomy were considered cases, while those who had not undergone episiotomy were admitted as controls. Women unable to give their informed consent (those in a coma, unconscious or mentally retarded) and who did not have an accompanying person with them who could consent to their participation in the study on their behalf were excluded from the study.

The dependent variable was having undergone episiotomy in any form (mediolateral or midline) and the independent variables were: a) maternal variables: age (years), parity, ethnicity (brown, black, white, yellow or indigenous), nutritional status evaluated according to body mass index (BMI), sociodemographic characteristics (place of origin and years of schooling); b) complications of pregnancy (diseases inherent to pregnancy or occurring during pregnancy), gestational age at delivery (weeks), previous Cesarean section, previous episiotomy; c) fetal characteristics: fetal presentation and fetal position during labor; d) external factors: the work shift, the professional attending delivery and the time of delivery; e) direct factors (related to delivery): induction or conduction of delivery, position at delivery (supine or other), type of delivery (spontaneous or instrumental), duration of expulsive phase, use of analgesia during delivery, presence of non-reassuring fetal heart rate, shoulder dystocia and fetal macrosomia.

The data were collected on standardized forms pre-coded for computer data entry. The statistical analysis was performed using the publicly available Epi-Info software program, version 7 (Atlanta, GA, USA). Measures of central tendency and dispersion and frequency distribution were used to describe the baseline characteristics. To determine the association between the dependent variable (episiotomy) and the independent variables (predictors), the chi-square test of association and Fisher's exact test were used, as appropriate, at a 5% significance level. The odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Multivariate analysis was carried out following a model of hierarchical multiple logistic regression<sup>10</sup> to determine the adjusted risk of episiotomy.

## RESULTS

During the study period, 2,563 vaginal deliveries were performed in the institute, with a frequency of episiotomy at around 10% (259 cases). Of these, 542 women were approached and 522 women agreed to participate in the study: 173 cases and 349 controls (Figure 1).



**FIGURE 1** Flow chart of the study.

The age of the women ranged from 13 to 44 years, with a mean of around 24 years of age. The median number of previous pregnancies and deliveries was 1, with a percentage of primiparas of 61.7%. The majority of the women (72%) had at least eight years of schooling and 45% came from the city of Recife. Mean gestational age at delivery was 37.6 weeks, with 29.5% of prematurity (< 37

weeks). Complications had occurred during pregnancy in around 52% of the participants, with a frequency of hypertensive syndromes of approximately 35%. Induction of labor with oxytocin was required in 55% of the women and 9.4% were submitted to instrumental delivery with the use of forceps (Table 1).

**TABLE 1** Baseline characteristics of the participants (n = 522)

Characteristic		
Age (range. mean $\pm$ SD)	13 - 44	23.9 $\pm$ 6
Previous pregnancies (range. median)	1 - 15	1
Previous deliveries (range. median)	1 - 12	1
Primiparas (n. %)	322	61.7
Schooling		
< 8 years of schooling	148	28.4
$\geq$ 8 years of schooling	373	71.6
Place of origin		
Recife	234	44.9%
Other towns	288	55.2
Gestational age at delivery (range. mean $\pm$ SD)	23 - 42	37.6 $\pm$ 2.9
Prematurity (n. %)	154	29.5
Complications in pregnancy	272	52.1%
Hypertensive syndromes	182	34.9%
Delivery induced (n. %)	286	54.8%
Instrumental delivery (n. %)	49	9.4%

**TABLE 2** Maternal and fetal factors associated with the use of episiotomy

Associated factors	Episiotomy				OR	95%CI	p-value
	Yes = 173		No = 349				
	n	%	n	%			
Maternal age < 20 years	64	37	63	20.9	2.22	1.48 - 3.32	0.00009
Primiparity	144	83.2	178	51	3.08	2.16 - 4.41	0.0000000
Black skin color	17	9.8	53	15.2	0.61	0.34 - 1.09	0.09
Overweight/obese	41	23.7	110	31.5	0.67	0.44 - 1.02	0.06
< 8 years of schooling	38	22	110	31.5	0.61	0.4 - 0.94	0.02
Lives in Recife	70	40.5	164	59.5	0.77	0.65 - 1.07	0.16
Prematurity	51	29.5	122	47	1	0.76 - 1.3	0.99
Complications during pregnancy	98	56.6	174	49.9	1.31	0.94 - 1.54	0.14
Previous cesarean section	9	5.2	20	5.7	0.9	0.4 - 2.03	0.8
Previous episiotomy	16	9.2	97	27.8	0.26	0.15 - 0.47	0.000002
Pelvic presentation	4	2.3	2	0.6	4.11	0.74 - 22.64	0.19*
Occipito-posterior position	22	28.6	41	36.9	0.68	0.36 - 1.28	0.23

95%CI: 95% confidence interval; OR: Odds Ratio.

\* Fisher's exact test (two-tailed).

Analysis of the maternal risk factors showed that the women submitted to episiotomy were more likely to be adolescents (OR = 2.22; 95%CI: 1.48 – 3.32) and primiparas (OR = 3.08; 95%CI: 2.16 – 4.41) and less likely to have fewer than eight years of schooling (OR = 0.61; 95%CI: 0.40 – 0.94) or a history of having had a previous episiotomy (OR = 0.26; 95%CI: 0.15 – 0.47). There was no association between episiotomy and the presence of complications during pregnancy ( $p = 0.14$ ), overweight/obesity ( $p = 0.06$ ), being black ( $p = 0.09$ ), coming from Recife ( $p = 0.16$ ), prematurity ( $p = 0.99$ ) or having had a previous Cesarean section ( $p = 0.80$ ). In relation to fetal risk factors, no association was found between episiotomy and pelvic presentation ( $p = 0.19$ ) or occiput posterior fetal position during labor ( $p = 0.23$ ) (Table 2).

With respect to the factors directly related to care at delivery, the women submitted to episiotomy were more likely to have had labor induced with oxytocin (OR = 1.92; 95%CI: 1.31 – 2.79), an instrumental delivery (OR = 18.91; 95%CI: 7.86 – 45.48), a prolonged expulsive phase (12% versus 0%, OR not calculated,  $p < 0.000001$ ), analgesia during labor (OR = 3.0; 95%CI: 1.77 – 5.08) and a diagnosis

of non-reassuring fetal heart rate (OR = 3.4; 95%CI: 1.82 – 6.37). There was no association between episiotomy and delivery in the supine position ( $p = 0.05$ ) or fetal macrosomia ( $p = 0.52$ ) (Table 3).

Regarding the external factors evaluated, the women submitted to episiotomy were three times more likely to have been attended by a staff physician (OR = 3.36; 95% CI: 1.97 – 5.72). On the other hand, delivery attended by nurses or resident nurses was found to constitute a protective factor against episiotomy (OR = 0.19; 95% CI: 0.10 – 0.35). There was no association between episiotomy and the day of the week or work shift (Table 3).

When multivariate analysis was performed using a hierarchical logistic regression model, the factors that remained significantly associated with a greater risk of episiotomy were primiparity (OR = 4.24; 95%CI: 2.61 – 6.89), instrumental delivery (OR = 12.31; 95%CI: 4.9 – 30.81) and delivery attended by a staff physician (OR = 1.88; 95%CI: 1.01 – 3.48), whereas a reduction in the risk was found when delivery was attended by a nurse (OR = 0.24; 95%CI: 0.16 – 0.55) (Table 4).

**TABLE 3** Intrapartum and external factors associated with the use of episiotomy

Associated factors	Episiotomy				OR	95% CI	p-value
	Yes = 173		No = 349				
	n	%	n	%			
Induction of delivery	113	65.3	173	49.6	1.92	1.31 – 2.79	0.0007
Supine position	81	46.8	195	55.9	0.69	0.48 – 1	0.05
Instrumental delivery	43	24.9	6	1.7	18.91	7.86 – 45.48	0.0000000
Prolonged expulsive phase	22	12	0	0	NE*	NE*	0.0000000
Analgesia at delivery	37	21.4	29	8.3	3	1.77 – 5.08	0.00002
Fetal distress	27	15.6	18	5.2	3.4	1.82 – 6.37	0.00006
Fetal macrosomia	5	2.9	9	2.6	1.12	0.37 – 3.41	>0.999999*
Sunday shift	33	19.1	46	13.2	1.32	0.98 – 1.77	0.08
Tuesday shift	18	10.4	44	12.6	0.81	0.45 – 1.44	0.23
Night shift	88	50.9	175	50.1	1.03	0.71 – 1.48	0.88
Delivery attended by medical staff	38	22	27	7.7	3.36	1.97 – 5.72	0.000005
Delivery attended by nurse or resident nurse	14	8.1	109	31.2	0.19	0.1 – 0.35	0.0000000

95%CI: 95% confidence interval; OR: Odds Ratio; NE= Not estimated.  
\* Fisher's exact test.

**TABLE 4** Multivariate analysis of the principal factors associated with episiotomy

Variable	Odds Ratio	95%CI	Coefficient	Standard Error	p-value
Delivery attended by nurse	0.29	0.16 – 0.55	-1.2248	0.32	0.0001
Instrumental delivery	12.31	4.9 – 30.81	2.5101	0.47	0.0000
Primiparity	4.24	2.61 – 6.89	1.4441	0.25	0.0000
Delivery attended by staff physician	1.88	1.01 – 3.48	0.6292	0.31	0.0457
Constant			-1.7816	0.22	0.0000

## DISCUSSION

The results of the present study suggest that the most important factors associated with episiotomy at IMIP are: primiparity, delivery attended by a staff physician and the use of forceps. In the case of women in whom episiotomy was not performed, their delivery was more likely to have been attended by nurses.

There was a 4-fold greater likelihood of episiotomy having been performed in primiparas. These results are in agreement with findings reported in the literature. One study conducted in the United States including 8,647 patients showed a frequency of episiotomy of 50% in primiparas compared to 23% in secundiparas and multiparas, a difference that was statistically significant.<sup>11</sup> Nevertheless, these data may reflect a more liberal practice of episiotomy in primiparas rather than any real need for the procedure in this group of women.

A clinical trial conducted in Venezuela showed no advantage in the routine use of episiotomy in primiparas<sup>12</sup> and the subgroup analysis in a Cochrane systematic review also did not favor the practice of episiotomy in primiparous women.<sup>2</sup> A large population-based, retrospective study including 2,315 primiparas and 534 multiparas concluded that episiotomy protected primiparas but not multiparas from the risk of an anal sphincter lesion; however, the indications for performing this procedure should be restricted, since 909 episiotomies would have to be performed to avoid one single case of anal sphincter rupture.<sup>13</sup>

The association found in the present study between fewer episiotomies and obstetric care provided by nurses was not surprising. In the systematic review available in the Cochrane Library, the risk of episiotomy was 20% lower in deliveries attended by midwives (20.7% *versus* 25.1%).<sup>14</sup> In the present study, the risk was much smaller, since fewer than 8% of deliveries in which episiotomy was performed were attended by nurses, while almost 30% were attended by physicians.

It could perhaps be argued that episiotomy is less likely to be performed by non-physicians because these pro-

fessionals only attend low-risk deliveries in which there is less need for episiotomy. Nevertheless, this explanation is not supported by the results of the present study, since a multivariate analysis was conducted and even after controlling for potentially confounding variables such as complications during pregnancy, a prolonged expulsive phase and instrumental delivery, deliveries at which episiotomy was performed were much less likely to have been attended by obstetric nurses. It is important to clarify that in the northeast of Brazil there are no university courses for midwives, which is why these professionals are not included in the childbirth care model used in this setting.

The important association between episiotomy and deliveries attended by staff physicians, but not those attended by medical residents, suggests that this procedure is strongly related to the amount of time the professional has been working in the area, since young medical residents are less likely to perform episiotomy. It is important to remember that the training of these new professionals is based on scientific evidence at a time in which the systematic practice of episiotomy in obstetrics is already being questioned. Deliveries involving episiotomy are almost twice as likely to have been attended by physician preceptors, many of whom graduated at a time in which the routine practice of episiotomy was not questioned.

As evidence accumulates on the lack of benefits of routinely performing episiotomy, we believe that young doctors will easily incorporate their critical judgment of this procedure into their clinical practice, unlike the physician preceptors who, despite the available evidence, are resistant to changes in conduct.

The association between episiotomy and forceps assisted deliveries was most evident in the present study, with a more than 12-fold likelihood of deliveries with an episiotomy having involved the use of forceps. It should be emphasized that the use of forceps or vacuum extraction used to be considered a classic indication for episiotomy. However, in addition to there being no

clear indication for episiotomy when an instrumental delivery is performed, the combination of an instrumental delivery and an episiotomy is believed to result in an increase in severe lacerations of the perineum, with possible damage to anal function. Recent studies recommend that this combination be avoided.<sup>14-16</sup> Even so, many professionals continue to believe that instrumental delivery constitutes an indication for episiotomy.

Indeed, it is rather unclear in which situations episiotomy is in fact indispensable. The Cochrane systematic review raised the question regarding the real indications for this procedure: operative vaginal delivery, preterm delivery, pelvic delivery, macrosomia or the risk of severe perineal laceration.<sup>2</sup> Consequently, a debate has ensued on whether these situations constitute indicators of a need for episiotomy and clearly require to be investigated further in new randomized clinical trials.<sup>17</sup>

With the objective of studying the factors that may affect whether or not this procedure is performed, in addition to the variables already mentioned, the present study also evaluated other factors such as pelvic presentation, prematurity, previous Cesarean section, non-reassuring heart rate, previous episiotomy, complications during pregnancy, macrosomia, induction of labor and/or the use of oxytocin during labor, and the use of analgesia during childbirth.

It was impossible to evaluate the association between episiotomy, shoulder dystocia, pelvic presentation and the diagnosis of a "risk of severe perineal laceration." Shoulder dystocia occurred in one single case and was not included as a variable in the analysis. Pelvic presentation occurred in six cases; however, there was no statistically significant association with episiotomy. On the other hand, "risk of severe perineal laceration" was not recorded on the women's medical charts as an indication for performing episiotomy, perhaps because this diagnosis is subjective. It is possible that some physicians may have performed episiotomy to protect the perineum against this risk of severe perineal laceration; however, there was no record of this indication on the medical charts. It should be emphasized that "risk of severe perineal laceration" is not an objective diagnosis and, clinically, the factors that characterize this event are not well defined.<sup>2,17</sup>

Although various authors have mentioned prematurity as an indication for episiotomy, with the objective of protecting the head of the fetus, in the present study no such association was found. Indeed, there are no clinical trials or observational studies corroborating the need for

episiotomy in premature deliveries or any evidence justifying the use of episiotomy to prevent fetal trauma at delivery.<sup>1,2,17</sup> On the contrary, a study evaluating 1,360 nulliparas submitted to forceps delivery or vacuum extraction showed that the use of episiotomy was associated with an increase in the rate of fetal contusions and skin abrasions, while having no effect on neonatal outcomes such as Apgar score, fetal acidosis or admission to a neonatal intensive care unit.<sup>15</sup>

History of a previous Cesarean section, characterizing a woman who has not yet delivered vaginally, was not associated with any increase in the risk of having an episiotomy, contrary to the findings of another study carried out in Pernambuco, Brazil.<sup>18</sup> On the other hand, having had a previous episiotomy was found to have a protective effect in the bivariate analysis, although this association was no longer present in the multivariate analysis.

Although the diagnosis of "non-reassuring heart rate" was associated with a greater risk of episiotomy in the bivariate analysis, this risk also failed to remain significant in the multivariate analysis. The intention of shortening the expulsive phase in cases in which anomalous fetal heart rate patterns are detected may have led some physicians to perform episiotomy. Another possible explanation is that when faced with a situation in which fetal vitality is compromised, some professionals may have opted to use forceps, and the majority of obstetricians still believe, as discussed previously, that episiotomy is fundamental when performing an instrumental delivery.<sup>1,14-17</sup>

With respect to macrosomia (fetal birth weight  $\geq 4$  kg) no statistically significant association was found with the practice of episiotomy. This fact may have occurred as a result of the obstetricians having no information on the weight of the concept prior to delivery. It should be emphasized that it is not routine practice in this service to perform ultrasonography at term for the purpose of predicting fetal weight, since the accuracy of this exam in detecting macrosomia is poor.<sup>19,20</sup> At any rate, studies suggest that episiotomy is not recommended either for the delivery of macrosomic fetuses or in situations in which shoulder dystocia occurs.<sup>17,21</sup> In fact, recent evidence shows that, even in the presence of conditions classically considered as "indications" for an episiotomy (macrosomia, non-reassuring heart rate, occipito-posterior position, shoulder dystocia and instrumental delivery), the risk of third and fourth degree lacerations was significantly greater when episiotomy was performed.<sup>22</sup>

In the bivariate analysis, both analgesia at delivery and induction with oxytocin were associated with episiotomy, although this association was no longer present in the mul-

tivariate analysis. There does not appear to be any direct association between the use of drugs to induce delivery or to provide analgesia and a need for an episiotomy; however, the presence of these variables may indicate a more interventionist approach by the professional attending delivery. Induced deliveries may also be more dystocic and may trigger a cascade of other interventions<sup>23</sup>. On the other hand, some professionals may find it simpler to perform an episiotomy in patients under analgesia; however, this may also lead to an increase in the duration of the expulsive phase and a greater risk of an instrumental delivery in patients receiving epidural analgesia.<sup>24</sup>

No association was found between episiotomy and complications such as preeclampsia, hypertension, diabetes and other conditions during pregnancy that would characterize it as high-risk. We believe that the presence of these factors may increase the risk of a Cesarean section, but they do not appear to affect the clinical decision to perform an episiotomy.

In relation to the position of the woman at delivery, positions other than the supine position (upright, lateral or hands-and-knees position) were less common in the group submitted to episiotomy (47% versus 56%), which is in agreement with the Cochrane systematic review suggesting that the risk of episiotomy is lower in non-supine positions.<sup>25</sup> Nevertheless, the association between the woman's position at delivery and episiotomy did not remain statistically significant in the multivariate analysis, probably because more important factors such as the professional attending the delivery were associated both with the choice of the woman's position for delivery and with the practice of episiotomy.

The rate of episiotomy at IMIP has fallen progressively over recent years and is currently at around 10%. Nevertheless, we believe that this rate can still be improved significantly, since most of the factors shown in the present study to be associated with the use of episiotomy are potentially modifiable. Stimulating care by nursing professionals at low-risk deliveries is fully possible and a measure that is recommended worldwide.<sup>14</sup> On the other hand, we believe that all the efforts made in the institute towards forming a new generation of physicians within a paradigm of evidence-based medicine have resulted in success, with a new generation of medical residents that has incorporated the concept that routine episiotomy is unnecessary.

For the future, we would suggest broadening the discussion on the actual indications for episiotomy and questioning the true role of episiotomy in pelvic and instrumental deliveries. Some authors have suggested that episiotomy may not be absolutely necessary in childbirth.<sup>17,22</sup>

Until the results of these future clinical trials become available, we suggest that efforts be made to restrict the practice of episiotomy and maintain rates within the limits suggested by the World Health Organization, i.e. 10% of deliveries. Both in individual and in institutional practice, it is important to document episiotomy rates and to recognize the factors associated with its practice in order to elaborate strategies to prevent unnecessary procedures that, in addition to being unwanted by women, may indeed be harmful to their health.<sup>2,3,5-8</sup>

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## RESUMO

Fatores de risco para a episiotomia: um estudo de caso-controle.

**Objetivo:** avaliar os fatores de risco para a episiotomia em mulheres grávidas que passaram por parto normal em uma maternidade de uma universidade no nordeste do Brasil.

**Métodos:** um estudo de caso-controle foi realizado com gestantes submetidas à episiotomia (casos) e mulheres grávidas não submetidas à episiotomia (controles) entre março de 2009 e julho de 2010, no Instituto de Medicina Integral Fernando Figueira (IMIP), Recife, Brasil, em uma proporção de um caso para dois controles. As variáveis do estudo foram: se episiotomia foi realizada, demográficas, obstétricas e características fetais (primiparidade, analgesia, parto instrumental, sofrimento fetal, etc.), fatores externos (dia e hora do parto, profissional que realizou o parto) e fatores diretamente relacionados ao parto. *Odds ratio* (OR) e intervalos de confiança de 95% (IC 95%) foram calculados. A análise multivariada foi realizada para determinar o risco ajustado de episiotomia.

**Resultados:** um total de 522 mulheres (173 casos e 349 controles) foi incluído. Verificou-se que os partos com episiotomia eram mais propensos a ter sido atendidos por médicos do *staff* (OR = 1,88, IC 95%: 1,01 - 3,48), necessidade de fórceps (OR = 12,31, IC 95%: 4,9 - 30,1) e ter ocorrido em primíparas (OR = 4,24, 95% CI: 2,61 - 6,89). A probabilidade de uma enfermeira ter assistido o parto com realização de episiotomia foi significativamente menor (OR = 0,29, 95% CI: 0,16 - 0,55).

**Conclusão:** a episiotomia foi considerada fortemente associada a partos assistidos por médicos da equipe, primiparidade e a parto instrumental, e foi menos comum em partos assistidos por enfermeiros.

**Palavras-chave:** episiotomia, parto normal, fatores de risco, períneo/lesões, estudos de casos e controles.

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# Microbiologic profile of hospitalized healthcare workers

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## SUMMARY

**Objective:** according to the epidemiologic and antimicrobial resistance profile, infections are usually classified as community-acquired or nosocomial. Reports on patients without the classic criteria for nosocomial infection with multidrug-resistant germs are increasing. There is a particular concern regarding which microbiological profile must be addressed in case of infections in healthcare workers. This study was carried out with the purpose of identifying the prevalence of infection by multidrug-resistant germs in healthcare workers exposed to occupational contact with such germs at work.

**Methods:** observational and retrospective study. In a 7-year period, healthcare worker hospitalizations were identified and the cultures results were assessed in order to identify the prevalence of infection by multidrug-resistant pathogens.

**Results:** 1,487 healthcare workers hospitalizations were identified. In 105 of these hospitalizations, cultures were collected on the first 5 days after admission, and in 22 patients, 24 germs were identified. Multidrug-resistant pathogens were not found.

**Conclusion:** in our sample, composed of workers from a tertiary public hospital who were hospitalized, none of the individuals presented MDR colonization or infection. These results suggest that when healthcare workers present infections, they must receive antibiotic therapy directed to community-acquired pathogens. In light of the limitations of this study, further larger and multicenter studies must be developed to enlighten such issue.

**Keywords:** nosocomial infection, antibacterial resistance, community-acquired infection, healthcare workers.

Study conducted at Hospital Nossa Senhora da Conceição

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## INTRODUCTION

Knowing the colonization profile of the population addressed is crucial to determine an empirical antibiotic therapy to be employed.<sup>1,2</sup> Historically, infections are defined as community-acquired (patients from extra-hospital setting) or nosocomial (acquired after at least 48 hours of admission or due to it), and empirical therapy is based on the germs commonly involved in each situation. More recently, the literature has used the expression “healthcare-associated infections”<sup>3,4</sup> to designate infections caused by multidrug-resistant organisms in outpatients with risk factors and exposure to MDRs, including those residing in

nursing homes, or who had extended contact with intra-hospital or hemodialysis facilities in the past 30 days, required hospitalization in emergency units for a period exceeding 48 hours in the last 90 days, or who underwent intravenous therapies in past 30 days.<sup>2-4</sup>

Recent reports have associated exposure to hospital germs to the development of infections by these pathogens. Thus, health professionals as well as patients with “infections associated with healthcare”, even without hospital admission, would be prone to colonization or infection with these germs. Because of that, it is argued which

single empirical antibiotic therapy would be correct in case of infection in a healthcare worker: empirical coverage directed to community germs or MDR bacteria?<sup>5-8</sup>

Based on that, defining the colonization profile of healthcare workers is a matter of great importance and aims to avoid prescription of inadequate empirical antibiotic therapy, which is associated with increased morbidity and mortality (if using limited spectrum antibiotic medication to treat patients with MDR bacteria), as well as the development of antimicrobial resistance within the population and unnecessary hospitalizations (in cases of improper use of broad-spectrum antibiotics).<sup>9-12</sup> To corroborate the elucidation of this question, we developed this retrospective observational study aimed to identify the microbiological profile of infections in healthcare professionals who required hospitalization.

## METHODS

An observational study was conducted through search of electronic medical charts at the Nossa Senhora da Conceição Hospital (HNSC), located in Porto Alegre, state of Rio Grande do Sul, Brazil. Admissions of employees of the Conceição Hospital Group (GHC), which includes the Nossa Senhora da Conceição Hospital, Cristo Redentor Hospital, Fêmeina Hospital, and the Conceição Children's Hospital, were identified retrospectively. The GHC is composed of tertiary level hospitals with endemic rates of colonization with MDR bacteria. All hospitalizations occurred at the Nossa Senhora da Conceição, since this is the hospital for clinical admissions in the GHC.

The population enrolled included workers of the GHC, admitted to the Nossa Senhora da Conceição Hospital in the period from January 2005 to January 2012, identified by means of their punch-in cards, regardless of the reason for hospitalization. Of these, patients with risk factors for colonization that did not arise from work activities were excluded: previous hospitalization for less than six months, with cultures collected after the fifth day of hospitalization, or with the absence of cultures. Data collection was initiated once the project was approved by the Research Ethics Committee-GHC, being performed from April to October 2012. The information was collected using searches for the following variables: gender, age, occupation (physician, nurse, nursing assistant/technician, or positions with no direct contact with patients), comorbidities, reason for hospitalization, ICU admission, and type outcome (hospital discharge *vs.* death).

Contact with MDR bacteria was defined based on occupation and sector of activity. Doctors, nurses or nursing technicians who worked in areas with high rates of infec-

tion or colonization with MDR bacteria, such as emergency rooms, ICUs, recovery rooms and wards, were regarded as professionals in contact with MDRs. Professionals who did not work in these sectors or who worked in these sectors performing activities without direct patient contact were considered as workers not in contact with MDRs. The reason for admission was classified as infectious or non-infectious and, in the case of infection, its focus was established. Patients with positive cultures who did not receive antibiotic treatment, on account of being asymptomatic despite bacterial growth on culture or whose medical charts did not mention infection, were defined as colonized patients (carriers). Empirical antibiotic therapy was considered adequate if the bacteria were sensitive to the antibiotic used. De-escalation of antimicrobial treatment after culture results was also assessed. Research sources were the admission form, the hospital discharge form and the outpatient consultation charts kept electronically by the hospital. The first chest radiography on admission was assessed. The chest X-ray was classified as compatible or not with bronchopneumonia, being compatible in case of new lobar consolidation, interstitial infiltrates or cavitating lesions. To define multidrug-resistant germs, we adopted the definition of ESKAPE pathogens previously created to emphasize the pathogens that most often correlate with hospital infections and that "escape" the effects of antibacterial drugs. They include: *Vancomycin*-resistant *enterococci*, *methicillin*-resistant *Staphylococcus aureus*, *Klebsiella* species and ESBL-producing *Escherichia coli*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and extended spectrum *beta-lactamase* (ESBL)- or *carbapenemase*-producing *Enterobacteriaceae*.<sup>13</sup> Importantly, the data were subjected to total secrecy, not allowing the identification of patients/staff. Since this was a retrospective chart review, no consent form was applied, as approved by the local ethics committee.

Statistical analysis was performed with SPSS 17.0 software (statistical package software, SPSS Incorporation, Chicago, IL, USA). The  $\chi^2$  was used to evaluate categorical variables and Student's *t* test for parametric continuous variables. For sample size calculation, the prevalence of positive cultures in 50% of the hospitalizations was estimated with a confidence level of 90%, being thus required the identification of 97 admissions.

## RESULTS

1,487 admissions of health workers were assessed in the study. In 1,155, there was no culture collection in the first five days of hospitalization, and in 227, the employee had already been hospitalized in the past six months. Of the 105 admissions with cultures collected in the first five

days, 83 were negative, and 22 hospitalizations had 24 bacteria isolated (Table 1 and Figure 1): *Escherichia coli* (10), *Coagulase-negative staphylococci* (CoNS,5), *Klebsiella pneumoniae* (2) and 7 other germs: *Enterococcus faecium*, *Enterococcus faecalis* (both sensitive to ampicillin), *Serratia marcescens*, *Staphylococcus epidermidis* (oxacillin susceptible), *Pseudomonas aeruginosa* (sensitive to quinolones, cefepime, piperacillin-tazobactam and carbapenems), *Streptococcus agalactiae* and *Cryptococcus neoformans*. Multiresistant bacteria were not isolated from any employee.

The profile of the sample is shown in Table 1. Among the 22 patients, 10 (45.5%) were nursing technicians and 12 (54.5%) had positions without direct patient contact: supervisors, administrative technicians, elevator operators, nutrition attendants, managers, pharmacy assistants, biomedical technicians, dispensers and cast technicians. There were no physicians or nurses in the sample. Based on workplace and job function, 10 employees had possible contact with MDR bacteria, 11 had no contact and 1 (4.5%) could not be determined.

Of the 22 admissions with bacterial isolates, 15 (68.2%) were hospitalizations due to infectious causes and 7 (31.8%), non-infectious. Thirteen patients received antibiotics. In 8 patients, the initial antibiotic therapy was considered appropriate to the pathogen, being maintained in 5 cases and de-escalated in 3, according to antibioticogram. In the other 2 patients, antibiotics were initiated after culture results. Among the 3 hospitalizations in which the empirical antibiotic therapy was considered inappropriate, one had the antibiotic therapy discontinued once the infection was attributed to *cryptococcal meningitis*, and in 2 the antibiotic therapy was adjusted after culture results (amoxicillin-clavulanate was replaced by piperacillin-tazobactam and metronidazole was replaced by cephalothin). The bacteria isolated in these cultures were *Pseudomonas aeruginosa* and *Staphylococcus epidermidis*, respectively. In the other 9 hospitalizations, antibiotics were not used because they were considered cases of colonization or sample contamination.

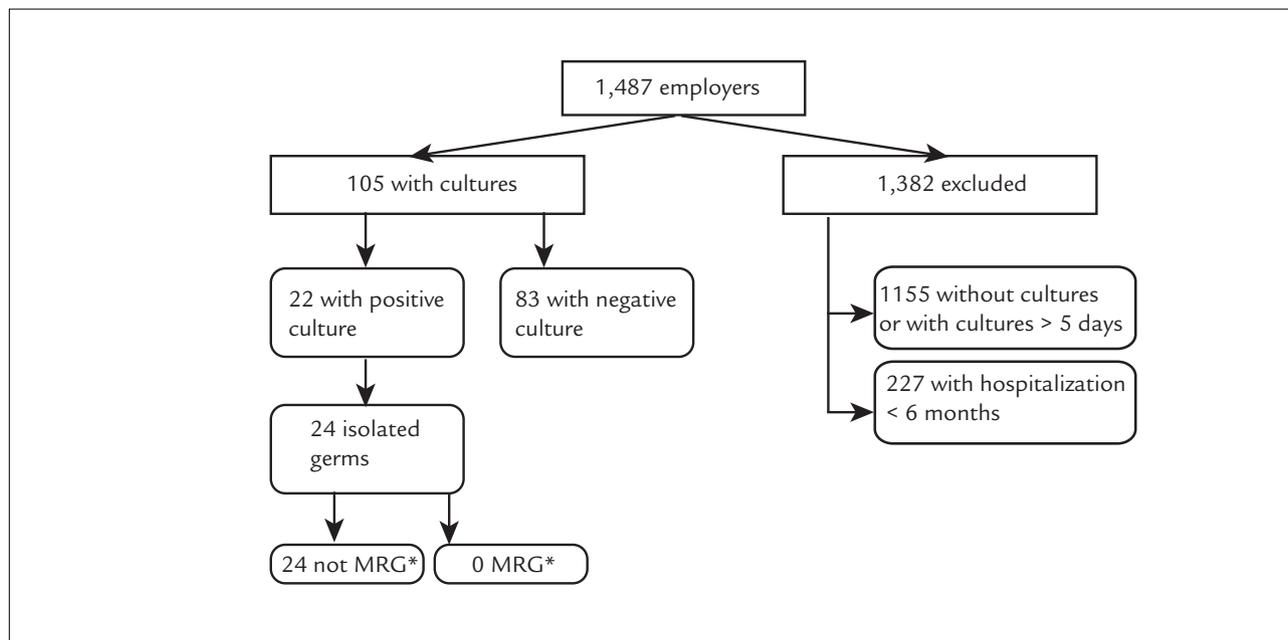
In this study, MDR bacteria were not found among the 24 cultures isolated from biological material taken from 22 employees of a general hospital. It is essential to point out that ten of these employees worked in areas with endemic presence of MDR bacteria. Reports prepared by the Commission of Hospital Infection at the Nossa Senhora da Conceição Hospital highlight the high pre-

**TABLE 1** Patient profile (n = 22)

	Results
<b>Age (years)</b>	49.3 ± 10.6
<b>Gender (F/M)</b>	13 (59%) / 9 (41%)
<b>Comorbidities</b>	
- Congestive heart failure	1 (4.5%)
- High blood pressure	7 (32%)
- Chronic obstructive pulmonary disease	1 (4.5%)
- Smoking	6 (27%)
- Diabetes mellitus	2 (9%)
- Acute renal failure requiring dialysis	1 (4.5%)
- Tuberculosis	2 (9%)
- Depression	3 (13.5%)
- Acquired immunodeficiency syndrome	1 (4.5%)
- Neoplasm	5 (23%)
<b>Occupation</b>	
- Nurse technician	10 (45%)
- Other positions	12 (55%)
<b>Microorganisms isolated</b>	
- <i>Escherichia coli</i>	10 (42%)
- <i>Coagulase-negative staphylococci</i>	5 (21%)
- <i>Klebsiella pneumoniae</i>	2 (8%)
- Other	7 (29%)
<b>Source of microorganism isolates</b>	
- Blood cultures	7 (31.8%)
- Urocultures	10 (45.5%)
- Sputum	1 (4.5%)
- Cerebrospinal fluid	1 (4.5%)
- Cutaneous abscess	1 (4.5%)
- Pulmonary lymph node	1 (4.5%)
- Abdominal fluid	1 (4.5%)
<b>Origin</b>	
- Respiratory	8 (36.4%)
- Abdominal	3 (13.6%)
- Urinary	9 (40.9%)
- Cutaneous	1 (4.5%)
- Central nervous system	1 (4.5%)
<b>Work location</b>	
- Hospital Nossa Senhora da Conceição	12 (54.5%)
- Hospital Cristo Redentor	6 (27.3%)
- Hospital Fêmeina	2 (9.1%)
- Conceição Children's Hospital	1 (4.5%)
- Not identified	1 (4.5%)

N = number of patients.

Results are expressed in absolute numbers (n) and percent (%) and mean ± standard deviation.



**FIGURE 1** Flowchart allocation of employees with hospitalization.

MRG: multidrug-resistant germs.

valence of germs such as *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* among local cultures, stressing local rates of imipenem resistance at 93% among isolates of *Acinetobacter baumannii* and 37% positivity for plasmid resistance for *Klebsiella pneumoniae carbapenemase* (KPC) in the genomic regions blaKPC-1 until blaKPC-7.<sup>14,15</sup>

Two microorganisms were isolated from urine culture and abdominal fluid samples. Of the pathogens isolated, 14 (58.3%) were considered infectious and 10 (41.7%) colonizing. Among the admissions analyzed, 3 (13.6%) refer to ICU stays and 1 (4.5%) progressed to death. The only healthcare worker admitted to ICU and who progressed to death was diagnosed with Acquired Immunodeficiency Syndrome and *Cryptococcus neoformans* isolated in CSF. Despite immunosuppression and ICU admission, this patient had no positive cultures for MDR bacteria.

## DISCUSSION

This study shows the largest sample described to date with profiles of colonization and infection in healthcare workers who required hospitalization. The result of our study suggests that health professionals, even when exposed to MDR bacteria, show no infections or colonization by such germs.

The current evidence on healthcare-associated infections suggests that the bacteria involved in this new classification have resistance profiles different from those commonly associated with community-acquired infections, in addition to being associated with higher morbidity and mortality.<sup>2,4,12,16,17</sup> Few studies that evaluate healthcare-associated infections address healthcare workers. Given the occupational exposure, it is important to study the microbiological profile of workers in the health segment. The few studies conducted in this context are limited to exceptional case reports describing rare events of direct transmission, with both patient and caretaker affected by the same pathogen.<sup>6,7</sup> Other reports have also associated infections in healthcare workers with certain scenarios from medical practice such as cardiopulmonary resuscitation rooms,<sup>18,19</sup> operating rooms<sup>20</sup> and intensive care units.<sup>21,22</sup> The report of unusual cases tends to wrongly magnify the fear of MDR infection in healthcare workers. Our sample seems more representative of the actual scenario: the incidence of infections in healthcare workers was low and mostly the clinical presentation did not reveal increased severity, being associated with community-acquired germs.

Importantly, in 83 workers who were hospitalized, the physician found it necessary to collect samples for culture, and this was done in the first 5 days after admis-

sion; nevertheless, no bacterial growth was found. This may have occurred for several reasons such as methodological limitation, technical issues, cultures collected after antibiotics were given, or possibly the absence of patient colonization/infection. We observed that in most patients hospitalized for infectious reasons, the causative germ was isolated. Some, though presenting active infection, had culture results suggestive of colonization, but the possible microorganism involved in the infection was not identified.

The average age of our sample was low (49 years) and predominantly comprised staff members without multiple comorbidities. The fact that these are individuals economically and socially active, also without relevant comorbidities, explains the low incidence of infections in this population and the lack of data regarding this topic, as well as the impossibility of carrying out prospective trials, either observational or clinical in nature.

Our study has several limitations. First, let us remember that this is a unicentric study. Therefore, we consider it relevant to the literature that many centers report the incidence of infections and the profile of antibacterial resistance in infections occurring in healthcare workers. The retrospective design and the definition of contact with MDRs derived from occupation and the identification of the work segment of the worker do not allow accurate determination of direct contact between the worker and carriers of MDR bacteria, even though the commission of hospital infection control in this group does report high rates of colonization with MDR bacteria in the wards.<sup>14</sup> Let us keep in mind that out of 1,487 admissions screened, only 22 had pathogens identified. As possible explanations, we can mention: a significant number of admissions due to non-infectious causes (individuals economically and socially active, with few comorbidities), the non-systematic collection of samples for cultures in the first five days from patients hospitalized with infection, the presence of recurrent hospitalizations, and negative cultures in the first 5 days. In our sample, the population was limited to nursing technicians and other occupations previously mentioned; doctors and nurses were not included. The fact that HNSC is a hospital that treats exclusively patients from the Brazilian Unified Health System (SUS public system) can in part justify this limitation, since those who can afford health insurance plans are usually admitted to the private network of hospital care. Likewise, some employees may have been hospitalized in other public hospitals, without our knowledge. Another possible limitation is due to the low number of infectious cultures in our sample,

since in many cases, even the blood cultures were characterized as colonizing.

## CONCLUSION

In our sample, composed of employees of a public tertiary care hospital with high rates of colonization by MDR undergoing clinical hospitalization, we found a low prevalence of both infections and colonization. Although evidence from the literature suggest that the antibiotic spectrum for empirical treatment of patients with healthcare-associated infections should be expanded, our results suggest that healthcare workers should not be included in this new classification when presenting infections. Thus, we suggest that antibiotic therapy is directed towards pathogens with resistance profiles of community-acquired bacteria, since no employee showed colonization or infection with MDRs. In light of the limitations of this study, further larger and multicenter studies must be developed to enlighten the issue.

## RESUMO

Perfil microbiológico de profissionais de saúde com internação hospitalar.

**Objetivo:** conforme perfil epidemiológico e resistência antimicrobiana, as infecções costumam ser divididas entre comunitárias e nosocomiais. É crescente o relato de pacientes sem critérios clássicos para infecções nosocomiais com infecções por germes multirresistentes (GMR). Há particular preocupação perante qual perfil microbiológico deve ser coberto na presença de infecções em profissionais de saúde. Realizamos este trabalho com intuito de identificar a prevalência de infecção por GMR em profissionais de saúde expostos a contato laboral com tais germes.

**Métodos:** estudo observacional, retrospectivo. Em um período de 7 anos, foram identificadas internações hospitalares de profissionais de saúde e aferidos resultados de culturas visando a identificar prevalência de infecção por GMR.

**Resultados:** identificamos 1.487 internações de profissionais de saúde. Em 105 internações, foram solicitadas culturas nos primeiros 5 dias de internação. Em 22 internações, foram identificados 24 germes. Não houve isolamento de GMR.

**Conclusão:** na amostra, composta por funcionários de um hospital público de nível terciário que apresentaram internação hospitalar, nenhum funcionário apresentou colonização ou infecção por GMR. O resultado sugere que trabalhadores da área de saúde, ao apresentar infecções,

devem receber antibioticoterapia voltada para patógenos comunitários. Tendo em vista as limitações deste estudo, são necessários estudos maiores e multicêntricos para elucidar essa questão.

**Palavras-chave:** infecção hospitalar; resistência antimicrobiana; infecção comunitária; pessoal da saúde.

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# Investigation of urinary abnormalities and risk factors for kidney disease in the World Kidney Day campaigns in Northeast Brazil

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## SUMMARY

**Objective:** chronic kidney disease (CKD) is an increasing common problem in the world due to the exponential growth of *diabetes mellitus*, hypertension and other risk factors. The aim of this study is to investigate urinary abnormalities and risk factors for kidney disease in the general population.

**Methods:** this study was performed from data collected during the annual World Kidney Day (WKD) campaigns, in Fortaleza, Ceará, Brazil, between 2009 and 2012. The population sought assistance spontaneously in stands placed in high people-traffic areas.

**Results:** among 2,637 individuals interviewed, the mean age was 50.7±15.7 years and 53% were male. The main risk factors found were sedentarism (60.7%), obesity (22.7%) and smoking (19.8%). Blood pressure (BP)  $\geq$  140x90 mmHg was found in 877 (33%). Increased BP was found for the first time in 527 cases (19.9%). Cardiovascular diseases were reported in 228 (8.6%). Diabetes was related by 343 (13%). Capillary blood glucose  $\geq$  200 mg/dL was found in 127 (4.8%) and it was  $\geq$  200 mg/dL for the first time in 30 (1.13%). Urinalysis was performed in 1,151 people and found proteinuria in 269 (23.3%). Proteinuria was most frequent in hypertension people (77.3% vs. 55.8%,  $p=0.0001$ ), *diabetes mellitus* (22.7% vs. 15.2%,  $p=0.005$ ) and elderly (42.1% vs. 30.7%,  $p=0.0007$ ).

**Conclusion:** risk factors for CKD are frequent in the general population. Many individuals had hypertension and diabetes and did not know this. It is important to regularly perform actions like WKD in order to early detect potential candidates for CKD.

**Keywords:** world kidney day, urinary abnormalities, chronic kidney disease, hypertension, *diabetes mellitus*.

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## INTRODUCTION

Chronic kidney disease (CKD) is an increasing common problem in the world. CKD is now a global public health problem due to the exponential growth of *diabetes mellitus*, hypertension and other risk factors.<sup>1</sup> By 2030, the number of people undergoing kidney replacement therapy in the United States is expected to increase to more than 2 million.<sup>1</sup>

Early detection of kidney disease offers the potential to improve outcomes by allowing for more time to intervene when most patients are still asymptomatic.<sup>2</sup> Abnor-

mal results identified during screening tests are not considered diagnostic but rather indicative of increased risk. There are few studies investigating renal dysfunction in the general population in Brazil. In a previous study conducted in the State of Minas Gerais, the prevalence of elevated creatinine was higher in the elderly.<sup>3</sup> In another study investigating the prevalence of CKD (stages 3, 4 and 5) in adults was 9.6%.<sup>4</sup>

End-stage renal disease (ESRD) has reached epidemic proportion with more than 400,000 affected individu-

als in the United States and over one million worldwide.<sup>5</sup> This staggering number represents only the tip of the iceberg, as the incidence of chronic kidney disease (CKD) is at least 30-fold higher than that of ESRD.<sup>6</sup>

The CARE project identified 56% of 348 individuals as at risk of diabetes, hypertension, and/or kidney disease and supported the feasibility of a regional targeted kidney disease screening action to identify individuals at risk.<sup>7</sup>

The aim of this study is to investigate urinary abnormalities and risk factors for kidney disease in the general population.

## METHODS

This study was performed from data collected during the annual World Kidney Day campaigns in Fortaleza, Ceará, Brazil, on 11<sup>th</sup> March 2009, 10<sup>th</sup> March 2010, 10<sup>th</sup> March 2011 and 8<sup>th</sup> March 2012. During the events, stands were placed in high people-traffic areas in which the population sought assistance spontaneously. The protocol of this study was approved by the ethics committee of the Federal University of Ceará, Brazil. A signed consent was obtained before filling out the forms.

The following data were collected: age, gender, weight, height and cardiovascular risk factors (smoking, physical inactivity, obesity and family history). Body mass index (BMI) was calculated using weight and height, and obesity was considered as BMI  $\geq 30$  kg/m<sup>2</sup>. Physical inactivity was considered when the individual reported expending less than 10% of their daily energy in the performance of moderate- and high-intensity activities.<sup>8</sup>

The following services were offered: guidelines for a healthy lifestyle, blood pressure and capillary blood glucose (with the equipment One touch ultra – Johnson & Johnson) measurement and urinalysis (dipstick Neocheck – Neomedica). Urinalysis was offered for each interviewed individual and it was performed for those who accepted to collect a urine sample.

Blood pressure was measured according to standard methods with free-mercury aneroid equipment (Welch Allyn – Tycos®). Patients were calmly seated in a chair for at least 5 minutes before their blood pressure was measured, their feet were placed on the floor and the arm where blood pressure would be measured was at the height of the heart. Patients had not drunk any coffee and had not smoked or made physical exercise 30 minutes before blood pressure was measured. A cuff of appropriate size was used. Two blood pressure measurements were done in the right arm, with 5 minutes interval, and the average was calculated.<sup>9</sup> The tests were performed by medical stu-

dents and professors of the Federal University of Ceará. Patients identified as having hypertension and/or diabetes were referred to the outpatients' clinics of the Walter Cantídio University Hospital.

Statistical analysis was performed using Epi-Info, version 6.04b. The results were expressed by means  $\pm$  standard deviation or relative frequencies. Comparison of parameters for two groups was done by means of Student's *t* test and Fisher's exact test. A comparison between patients with and without proteinuria was done. Descriptive values below 5% ( $p < 0.05$ ) were considered statistically significant.

## RESULTS

A total of 2,637 individuals were interviewed. The mean age was  $50.7 \pm 15.7$  years and 53% were male. The main cardiovascular risk factors found were sedentary lifestyle (60.7%), obesity (22.7%) and smoking (19.8%). Previous diagnosis of hypertension was related by 906 (34.3%) individuals. Blood pressure higher than 140/90 mmHg was found in 877 (33%) participants. First finding of increased blood pressure was found in 527 (19.9%). Cardiovascular diseases were reported in 228 (8.6%). Diabetes was related by 343 (13%) individuals. Capillary blood glucose higher than 200 mg/dL was found in 127 (4.8%) and it was higher than 200 mg/dL for the first time in 30 cases (1.13%). The majority of the interviewed (38.6%) presented capillary blood glucose between 100 and 126 mg/dL. Urinalysis was performed in 1,151 patients and found proteinuria in 269 cases (23.3%). *Proteinuria* was most frequent in patients with hypertension (77.3% vs. 55.8%,  $p = 0.0001$ ), diabetes mellitus (22.7% vs. 15.2%,  $p = 0.005$ ) and elderly individuals (42.1% vs. 30.7%,  $p = 0.0007$ ).

## DISCUSSION

There are few studies investigating the prevalence of CKD in the general population. Our study tried to identify risk factors for renal dysfunction in the general population in a metropolitan area in Brazil, mainly hypertension, *diabetes mellitus* and *proteinuria*. The National Kidney Foundation's Kidney Early Evaluation Program (NKF KEEP) identifies individuals at increased CKD risk by using inclusion and exclusion criteria.<sup>10</sup> People are included if they have at least one of the following criteria: hypertension, diabetes and family history of hypertension, diabetes and chronic kidney disease. Individuals undergoing renal replacement therapy or kidney transplantation were excluded. The overall CKD prevalence found was 29% and only 7% self-reported CKD, demonstrating low CKD awareness in general population.<sup>10</sup>

In the present study with 2,637 individuals, the mean age was 51 years and 53% were male. NKF KEEP included 61,675 participants with 54 years and 68% were female.<sup>10</sup> KEEP Japan included 1,065 participants with 60 years old and 53% were female.<sup>11</sup> In KEEP Mexico, 1,519 individuals participated and more than 70% were female.<sup>12</sup>

High blood pressure was found in 33% of measurements and first finding of increased blood pressure was found in 20% of subjects in our study, which means that an important proportion of patients had hypertension and did not know it. Among NKF KEEP participants, 66% have increased blood pressure, 17% have isolated measured hypertension and 53% have self-reported hypertension.<sup>10</sup> Hypertension was self-reported in 59%<sup>10,11</sup> and in 62% in KEEP Mexico.<sup>12</sup>

In our cohort, diabetes was related by 13%. Capillary blood glucose higher than 200 mg/dL was found in 5% and it was higher than 200 mg/dL for the first time in 1%, which can be considered as diagnosis of diabetes. NKF KEEP data found that 30% of participants have diabetes, self-reported (25%) or based on glucose testing alone (5%)<sup>10</sup>. Fifty percent of NKF KEEP participants who self-reported diabetes have a high measured glucose level. In KEEP Japan, 27% self-reported diabetes. Glycemic control was higher than 139 mg/dL for 35% of diabetic participants. High blood glucose was newly found in 21 participants.<sup>11</sup>

Among all participants, 20.8% in KEEP Japan and 21.2% in NKF KEEP self-reported one or more cardiovascular diseases.<sup>10,11</sup> In the present study, these conditions were reported in 9% of individuals.

Urine protein, determined by the dipstick method, was positive for 7.2% in KEEP Japan.<sup>11</sup> Abreu et al.<sup>13</sup> found 26% of *hematuria* e 5% of *proteinuria* among 200 elderly subjects in São Paulo, Brazil. Different from others reports, in the present study, urinalysis was performed in 1,151 individuals and found a high level of *proteinuria* (23.3%).

This study has some limitations. The findings may not be generalizable to the total Brazilian population as the study includes only self-referred population. We could not estimate glomerular rate filtration because there was no measurement of *serum creatinine*. A single measurement of blood pressure in health campaigns does not allow diagnosing hypertension nor preclude the possibility of white-coat effect.

Lack of health insurance is an independent risk factor for early death and ESRD in individuals with high risk of kidney disease.<sup>14</sup> The goals of early CKD detection are to prevent CKD progression and associated compli-

cations, thus improving patient outcomes. Campaigns are important to warn people who may be at risk of developing hypertension and for those who already have hypertension and had not yet been diagnosed.

In summary, risk factors for CKD are frequent in the general population. Many individuals had hypertension and diabetes and did not know it. It is important to regularly perform actions like WKD in order to early detect potential candidates for CKD. Campaigns like World Kidney Day have a good cost-effectiveness ratio because in the absence of more elaborated studies to evaluate the prevalence of CKD they act as an alert to the population of the risk of hypertension and diabetes, mainly in people with family history, overweight, obesity, sedentarism and other risk factors for renocardiovascular diseases. Studies like this are important to early detect risk factors for renal function loss and to adopt measures to slow the progression of kidney disease. These measures can impact public health since fewer patients would need renal replacement therapy if kidney disease is detected in early stages.

**TABLE 1** Epidemiological characteristics and risk factors for chronic kidney disease in 2,637 individuals in Northeast Brazil

	N	%
<b>Age, years</b>		
18-30	312	11.8
31-45	674	25.5
46-60	891	33.7
61-75	618	23.4
>75	142	5.3
<b>Gender</b>		
Male	1235	47
Female	1402	53
<b>Risk factors</b>		
Smoking	523	19.8
Physical inactivity	1601	60.7
Obesity	599	22.7
Cardiovascular diseases	228	8.6
Proteinuria	269	23.3

**TABLE 2** Urinary findings in 1,151 in participants Northeast of Brazil

	N	%
Proteinuria	269	23.3
Leukocyturia	144	12.5
Hematuria	38	3.3

**TABLE 3** Comparison of individuals with and without proteinuria among 1,151 participants in Northeast Brazil

	With proteinuria (n = 269)	Without proteinuria (n = 882)	P
Age, years	54.3±15.8	51.4±14.5	0.005
Gender			
Male (%)	117 (43.5)	393 (44.6)	
Female (%)	152 (56.5)	489 (55.4)	0.77
Smoking (%)	64 (23.7)	204 (23.1)	0.86
Obesity (%)	80 (29.7)	234 (26.5)	0.30
Sedentarism (%)	172 (63.9)	556 (63)	0.82
Diabetes mellitus (%)	56 (20.8)	120 (13.6)	0.005
CBG ≥ 200 mg/dL (%)	5 (1.8)	14 (1.5)	0.78
Hypertension (%)	155 (57.6)	318 (36)	0.0001
BP ≥ 140x90 mmHg	53 (19.7)	175 (19.8)	1.0
SBP (mmHg)	138±22	129±19	0.0001
DBP (mmHg)	85±12	82±11	0.0001
Cardiovascular diseases (%)	33 (12.2)	34 (3.8)	0.0001
Renal diseases family history (%)	44 (16.3)	71 (8.0)	0.0002
BMI (kg/m <sup>2</sup> )	28.1±4.8	27.5±4.5	0.05

CBG = Capillary blood glucose, BP = blood pressure, SBP = systolic blood pressure, DBP = diastolic blood pressure, BMI = body mass index. Values expressed as mean ± SD. Significant P < 0.05.

## RESUMO

Investigação de alterações urinárias e fatores de risco para doença renal nas campanhas do Dia Mundial do Rim no nordeste do Brasil.

**Objetivo:** a doença renal crônica (DRC) é um problema crescente no mundo em razão do crescimento exponencial do *diabetes mellitus*, da hipertensão e de outros fatores de risco. O objetivo deste estudo é investigar alterações urinárias e fatores de risco para doença renal na população geral.

**Métodos:** este estudo foi realizado a partir de dados coletados durante as campanhas anuais do Dia Mundial do Rim, em Fortaleza, Ceará, Brasil, entre 2009 e 2012. A população buscou atendimento espontaneamente nos *stands* montados em locais de alto tráfego de pessoas.

**Resultados:** entre 2.637 indivíduos entrevistados, a média de idade foi de 50,7±15,7 anos, sendo 53% do gênero masculino. Os principais fatores de risco encontrados foram sedentarismo (60,7%), obesidade (22,7%) e tabagismo (19,8%). Pressão arterial (PA) ≥ 140x90 mmHg foi encontrada em 877 casos (33%). Aumento da PA foi encontrado pela primeira vez em 527 casos (19,9%). Doenças cardiovasculares foram relatadas por 228 indivíduos (8,6%). Diabetes foi relatado por 343 indivíduos (13%). Glicemia capilar ≥ 200 mg/dL foi encontrada em 127 ca-

sos (4,8%) e ≥ 200 mg/dL pela primeira vez em 30 (1,13%). O exame de urina foi realizado por 1.151 pessoas, sendo encontrada proteinúria em 269 casos (23,3%). Proteinúria foi mais frequente em pessoas com hipertensão (77,3% vs. 55,8%, p = 0,0001), *diabetes mellitus* (22,7% vs. 15,2%, p = 0,005) e em idosos (42,1% vs. 30,7%, p = 0,0007).

**Conclusão:** fatores de risco para DRC são frequentes na população geral. Muitos indivíduos tinham hipertensão e diabetes e não sabiam disso. É importante a realização de ações como o Dia Mundial do Rim com o objetivo de detectar precocemente potenciais candidatos à DRC.

**Palavras-chave:** Dia Mundial do Rim; alterações urinárias; doença renal crônica; hipertensão; *diabetes mellitus*.

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# How to evaluate quality of life in overweight and obese women during climacterium?

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## SUMMARY

**Objective:** identifying the instruments used to measure quality of life during menopausal transition and post-menopause in women with obesity or overweight.

**Methods:** a systematic search using the Embase, Pubmed and Cochrane databases, and the following key-words: menopause/climacteric, quality of life, overweight/obesity. Nineteen papers that fulfilled the including criteria were found.

**Results:** eighteen studies using generic health questionnaires (global quality of life) were identified, six of them were specific for menopause and one specific for obesity. Eleven studies used generic questionnaires, while only eight questionnaires were specific for menopause.

**Conclusion:** there was no consensus in the literature about the use of quality of life questionnaires in women with overweight and obesity in climacterium, which makes de comparison and reproducibility of the results difficult. This is an alert about the need for standardization to better evaluate this specific population.

**Keywords:** menopause, climacteric, overweight, obesity, quality of life.

## INTRODUCTION

Obesity is a multifactorial disease, epidemic in nature, which according to the World Health Organization affects over 300 million adults worldwide. Overweight individuals correspond to about one billion adults.<sup>1</sup> The body mass index (BMI) of women seems to reach its highest values between 50 and 59 years, a period that often coincides with menopause.<sup>2</sup>

This period is characterized by body aging linked to progressive hypoestrogenism, which not only triggers health implications, but is also associated with changes in women's lives. Characteristic symptoms may be observed, including vasomotor, psychological, urogenital, sleep disturbances and sexual dysfunction, as well as difficulties in emotional and social sphere.<sup>3-6</sup> The quality of life

in postmenopausal women is a major subject, because its results can help define therapeutic approaches and promote healthier aging for females, with improved quality of life.<sup>4,5,7</sup>

Research shows associations among obesity, menopausal symptoms and worse quality of life.<sup>5,8-17</sup> To conduct this evaluation, various types of questionnaires are used, both generic - analyzing overall quality of life for any population - and specific questionnaires to analyze the quality of life in the transition to menopause and postmenopause.<sup>18-21</sup>

The objective of this work is to identify the instruments used to measure the quality of life of overweight and obese women in climacteric age (during the transi-

tion to menopause and post-menopause), through a systematic review of the literature.

## METHODS

A systematic search was performed using the Embase, Pubmed and Cochrane databases, and the following keywords: menopause/climacteric, quality of life, overweight/obesity. Full articles and editorials in English, Portuguese and Spanish were selected. Inclusion criteria were: full articles that used at least one questionnaire to assess quality of life or questionnaire related to climacteric symptoms, being at least part of the sample comprised of patients with overweight, obesity or metabolic syndrome who were also in transition to menopause and post-menopause. Exclusion criteria were: case reports and systematic reviews. Using these criteria were selected twenty-two articles after reading the title and abs-

tract. After reading the full articles, three were excluded for the following reasons: the first examined only psychological well-being, the second used questionnaires of quality of life specific to women with breast cancer, and the third used specific questionnaires for urinary incontinence and sexual function. In the end, 19 articles were selected for this systematic review.

## RESULTS

Nineteen articles were found in the systematic literature search. The characteristics of both the articles and questionnaires used are summarized in Table 1. The studies were published between 1999 and 2013, and ten of these were dated 2009 or later. The different populations ranged from 40 to 70 years of age, n ranged from 30 to 161.393 women, with the majority (13) of research having n of 200-1,194.

**TABLE 1** Summary of articles that used questionnaires to assess quality of life in overweight or obese women in transition to menopause and post-menopause, identifying the year of publication, the instrument used, age range and/or mean population and number of participants

Year	Author	Instruments	Age (mean)	n
2013	Ashok P et al. <sup>22</sup>	World Health Organization five-item well-being index (WHO-5)	40-60	60
2012	Gallon CW et al. <sup>33</sup>	Menopause Rating Scale (MRS)	40-65 (52.8)	200
2011	Imayama I et al. <sup>23</sup>	SF-36; Brief Symptom Inventory-18; Perceived Stress Scale; Social Support Survey	50-75 (58)	439
2011	Heidelberg DA et al. <sup>24</sup>	SF-12	35-74	983
2010	Lynch CP et al. <sup>25</sup>	Items taken from instruments used in the WHI trial to assess emotional aspects of quality of life; SF-36 to evaluate physical aspects of quality of life	50-79	161,393
2010	Alonso AMF et al. <sup>9</sup>	Kupperman Index	(49.9)	574
2010	Riesco E et al. <sup>26</sup>	SF-36	Pre-menopausal women (49) Post-menopausal women (52)	30
2009	González FG et al. <sup>27</sup>	EuroQol 5-D; Rosenberg Self-Esteem Scale	(60.53)	106
2009	Castelo-Branco C et al. <sup>34</sup>	Cervantes Scale	45-64 (54.38)	284
2009	Llaneza P et al. <sup>35</sup>	Cervantes Scale	50-65	496
2009	Messier V et al. <sup>28</sup>	Medical Outcomes Study General Health Survey (MOS)	46-70	136
2008	Karelis AD et al. <sup>29</sup>	Medical Outcomes Study General Health Survey (MOS); Perceived Stress Scale; Self-Esteem Scale; Body-Esteem Scale; Scale of perceived risk for developing heart disease or diabetes	46-70	137
2008	Yankura DJ <sup>30</sup>	SF-36	52-62	580
2007	Llaneza P et al. <sup>36</sup>	Cervantes Scale	50-64	250
2007	Lemoine S et al. <sup>31</sup>	SF-36; Three-Factor Eating Questionnaire	Pre-menopausal women 30-45(39) Post-menopausal women 49-64 (56)	40
2007	Daley A et al. <sup>37</sup>	Women's Health Questionnaire (WHQ)	46-55 (50.5)	1,194
2007	Chedraui P et al. <sup>38</sup>	MENQOL	40-70 (55.9)	325
2006	Mirzaiinjtabadi K et al. <sup>39</sup>	Greene Scale	45-60	883
1999	Raikkonen K et al. <sup>32</sup>	SF-36; Beck Depression Inventory; Spielberg Trait Anger/Anxiety Questionnaire; Scale for distress; Interpersonal Support Evaluation List (ISEL)	45-53	345

Twenty-four questionnaires were identified in nineteen articles (Table 2). The instruments found were divided into generic, assessing overall quality of life in any population; specific, for quality of life in women during transition to menopause and post-menopause; and restricted, for psychosocial aspects of quality of life.

**TABLE 2** List of assessment tools for quality of life used in overweight and obese women in transition to menopause and post-menopause, identifying the type of instrument, frequency of use, and year of use

Instrument	Type	Frequency	Year
World Health Organization five-item well-being index (WHO-5)	EPS	1	2013
Menopause Rating Scale (MRS)	EM	1	2012
SF-36	G	6	2011, 2010, 2010, 2008, 2007, 1999
Brief Symptom Inventory-18	EPS	1	2011
Social Support Survey	EPS	1	2011
SF-12	G	1	2011
Perceived Stress Scale	EPS	2	2008, 2011
Items taken from instruments used in the WHI trial	EPS	1	2010
Kupperman Index	EM	1	2010
EuroQol 5-D	G	1	2009
Rosenberg Global Self-Esteem Scale	EPS	1	2009
Cervantes Scale	EM	3	2009, 2009, 2007
Medical Outcomes Study General Health Survey (MOS)	G	2	2009, 2008
Self-Esteem Scale	EPS	1	2008
Body-Esteem Scale	EPS	1	2008
Scale of perceived risk for developing heart disease or diabetes	EPS	1	2008
Three-Factor Eating Questionnaire	EPS	1	2007
Women's Health Questionnaire (WHQ)	EM	1	2007
MENQOL	EM	1	2007
Greene Scale	EM	1	2006
Beck Depression Inventory	EPS	1	1999
Spielberg Trait Anger/Anxiety Questionnaire	EPS	1	1999
Scale for Distress	EPS	1	1999
Interpersonal Support Evaluation List (ISEL)	EPS	1	1999

G: generic quality of life instrument; EM: specific instrument for quality of life in the transition to menopause and post-menopause; EPS: specific instrument for psychosocial aspects of quality of life.

Four different instruments were identified to assess overall quality of life. For specific analysis of quality of life related to the climacteric period, six different questionnaires were used. Most instruments found (fourteen) aimed to quantify the quality of life related to psychosocial aspects.

The SF-36 was observed more frequently, being used in six articles published from 1999 to 2011. The second most frequently found was the Cervantes Scale, seen in three articles, two published by a single group of researchers (Lhaneza et al.<sup>35,36</sup>). The Medical Outcome Study General Health Survey (MOS) was used in two articles, and the other questionnaires in one study only.

Six studies used more than one instrument to measure quality of life. Eight studies used specific questionnaires for menopause, while 11 used generic questionnaires, combined or not with instruments for psychosocial analysis.

## DISCUSSION

The nineteen studies obtained used twenty-four different scales. Eleven used generic questionnaires,<sup>22-32</sup> while eight employed specific instruments to assess quality of life in women before and after menopause.<sup>9,33-39</sup> A single article made reference to a specific questionnaire related to obesity.<sup>31</sup>

The SF-36 and Medical Outcomes Study General Health Survey (MOS) questionnaires, which are derived from the same study, were the most prevalent generic tools, being found in eight articles.<sup>23,25,26,28-32</sup> The SF-36 was the most widely adopted, being found in six articles,<sup>23,25,26,30-32</sup> which is consistent with the literature, since it is the most widely used generic instrument documented in over four hundred publications.<sup>40,41</sup> However, none of these questionnaires takes into consideration important aspects such as menopausal symptoms or specific psychosocial conditions regarding this time of life, which hinders the assessment of quality of life in this population. The social psychological aspect was measured by fourteen different scales covering aspects of emotional health and the social structure in which the individual lives, which affect the quality of life. Six articles used generic instruments combined with psychosocial questionnaires, showing that the use of generic instruments may fail to take into account important aspects of quality of life in the period close to menopause.<sup>23,25,27,29,31,32</sup>

Ashok et al.<sup>22</sup> used the World Health Organization five-item well-being index (WHO-5) well-being questionnaire, which assesses psychological and not physical dimensions related to menopause.<sup>22</sup> Lynch et al.<sup>25</sup> used the SF-36 together with a questionnaire to determine psychosocial quality of life created from instruments used in the

Women's Health Initiative (WHI) trial.<sup>25</sup> Therefore, the article used its own instrument, unlike those classically found in the literature, which demonstrates the lack of standardization in the literature.

Eight of the nineteen studies used specific questionnaires for menopause.<sup>9,33-39</sup> The Cervantes Scale was the most prevalent, found in three of them.<sup>34-36</sup> The instrument was developed in Spanish, mainly for use in this population, and translated into Portuguese, despite being validated in a limited number of countries.<sup>42</sup> In these three studies, two were conducted by the same author (Llaneza et al.<sup>9</sup>, making it difficult to generalize the results.<sup>35,36</sup> Alonso et al.<sup>39</sup> used the Kupperman Index, according to the data found in the literature about its widespread use, even with criticism for not addressing urogenital, social and other symptoms related to sexuality.<sup>9,43-45</sup> Mirzaiinjabadi et al.<sup>39</sup> used the Greene Scale, a list of 21 items including psychological, vasomotor and somatic symptoms, which was not exactly designed as an instrument of quality of life.<sup>21,39</sup> The other specific questionnaires were: Menopause Rating Scale (MRS), Women's Health Questionnaire (WHQ) and Menopause-Specific Quality of Life Questionnaire (MENQOL), which have already been validated and are the main scales currently used in studies on women in transition to menopause and post-menopause.<sup>33,37,38,43,46,47</sup> In Brazil, only WHQ, MENQOL and Cervantes Scale were validated; Greene Scale has been used for many years, and MRS is being used even without validation.

Lemoine et al.<sup>31</sup> was the only author who used a specific questionnaire for obesity, the Three-Factor Eating Questionnaire, which is related to psychological well-being. Thus, it is important to assess the need to use specific questionnaires for obesity since the population in question is also subject to the effects of obesity as a comorbidity on quality of life.<sup>31</sup>

There is no consensus as to the best type of instrument to be used to assess quality of life. Fayers et al.<sup>41</sup> believes that both generic and specific measures have advantages and disadvantages. He recommends the use of generic and specific instruments wherever possible, in combination, to give strength to both approaches.<sup>41</sup> On the other hand, many researchers prefer to use specific questionnaires to assess a certain condition. Chedraui et al.<sup>38</sup> states that specific instruments are required in each condition, and menopause, or climacterium, is not an exception.<sup>38</sup> Utian<sup>16</sup> believes that in order to evaluate the quality of life of women in transition to menopause and post-menopause, somatic symptoms such as hot flashes, night sweats, genital atrophy and urinary incontinence, and psychological symptoms such as mood swings and

life circumstances, should be included; i.e., occupational, sexual, emotional and health-related factors.<sup>16</sup> Schneider et al.<sup>21</sup> argues that the instrument must have certain attributes or properties of measures suitable for a particular purpose. Specific questionnaires are more sensitive to change and make sense for both the physician and patient, since the items included report highly relevant domains to that particular population.<sup>21</sup>

The varied use of questionnaires can be justified by the researcher's choice for the most widely used instruments such as the SF-36 and also the preference of certain authors to use surveys created in the language and targeted to the cultural context of the study population.<sup>48</sup> The predilection for generic tools found in the articles used in this review fails to analyze important characteristics of the study population, given the peculiarities of both the period of transition to menopause and post-menopause and obesity. Therefore, assessment of the quality of life of these women was hindered.

## CONCLUSION

The most widely used instrument for assessing quality of life in obese women in transition to menopause and post-menopause was the generic SF-36 questionnaire. The Cervantes Scale was the specific instrument most used. There was no consensus regarding the use of the instruments, which is an obstacle for comparison and reproducibility of results. The current study is a warning to researchers that there is a need for a standard instrument to assess this growing population.

## RESUMO

Como aferir qualidade de vida de mulheres com sobrepeso e obesidade no climatério?

**Objetivo:** identificar os instrumentos utilizados para aferir a qualidade de vida de mulheres com sobrepeso e obesidade no climatério (transição para menopausa e pós-menopausa).

**Métodos:** busca sistemática nas bases de dados Embase, Pubmed e Cochrane com os descritores: *menopause/climacteric, quality of life, overweight/obesity*. Foram incluídos 19 artigos que preencheram os critérios de inclusão.

**Resultados:** foram identificados 18 questionários genéricos (qualidade de vida global), 6 específicos para menopausa e 1 específico para obesidade. Onze estudos utilizaram instrumentos genéricos, enquanto 8 utilizaram específicos para menopausa.

**Conclusão:** não houve consenso na literatura quanto ao uso de instrumentos de qualidade de vida em mulheres com sobrepeso e obesidade no climatério, o que dificultou a comparação e a reprodutibilidade dos resultados. Este é um alerta quanto à necessidade de padronização para melhor avaliar essa população específica.

**Palavras-chave:** menopausa; climatério; sobrepeso; obesidade; qualidade de vida.

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# Waldenström's macroglobulinemia – a review

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## SUMMARY

Waldenström's macroglobulinemia (WM) is a lymphoproliferative disease of B lymphocytes, characterized by a lymphoplasmocytic lymphoma in the bone marrow and by IgM monoclonal hypergammaglobulinemia. It was first described in 1944 by Jan Gösta Waldenström, reporting two patients with oronasal bleeding, lymphadenopathy, anemia, thrombocytopenia, high erythrocyte sedimentation rate and serum viscosity, normal radiography and bone marrow infiltrated by lymphoid cells.

The WM is a rare disease with a typically indolent clinical course, affecting mainly individuals aged between 63 and 68 years. Most patients have clinical signs and symptoms related to hyperviscosity resulting from IgM monoclonal gammopathy, and/or cytopenias resulting from bone marrow infiltration by lymphoma. The differential diagnosis with other lymphomas is essential for the assessment of prognosis and therapeutic approach.

Treatment of patients with asymptomatic WM does not improve the quality of life of patients, or increase their survival, being recommended, therefore, their follow-up. For the treatment of symptomatic patients, alkylating agents, purine analogs and anti-CD20 monoclonal antibodies are used. However, the disease is incurable and the response to therapy is not always favorable. Recent studies have shown promising results with bortezomib, an inhibitor of proteasomes, and some patients respond to thalidomide. In patients with relapse or refractory to therapy, autologous transplantation may be indicated.

The aim of this paper is to describe in detail the current knowledge on the pathophysiology of WM, main clinical manifestations, diagnosis, prognosis and treatment.

**Keywords:** Waldenström's macroglobulinemia, hypergammaglobulinemia, IgM, lymphocytes B. prognosis.

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## INTRODUCTION

Waldenström's macroglobulinemia (WM), described in 1944 by Jan Gösta Waldenström, is a lymphoplasmacytic lymphoma (LPL) characterized by IgM monoclonal hypergammaglobulinemia and bone marrow infiltration.<sup>1</sup>

LPLs are rare and indolent cancers of mature B-lymphocytes, which predominantly involve the bone marrow and, less commonly, the spleen, lymph nodes, peripheral blood and other organs.<sup>1</sup>

## EPIDEMIOLOGY

WM has an estimated incidence of 3 cases/million/year, accounting for about 2% of all hematological cancers.<sup>2</sup>

There is a higher incidence in individuals aged between 63 and 68 years.<sup>3</sup> Approximately 60% of patients are men, and it is more common in caucasian individuals.<sup>3</sup> The average survival is 5 years,<sup>3</sup> however, approximately 10% of patients survive up to 15 years.<sup>4</sup> As the disease is mainly diagnosed in old age, about 50% of patients die due to comorbidities not related directly to WM.<sup>3</sup>

## ETIOLOGY

Its etiology is unknown, but several studies suggest a possible causal relationship with autoimmune diseases, exposure to environmental factors and chronic antigenic

stimulation, such as infection with the hepatitis C virus (HCV). Despite the high incidence of HCV infection in these patients, a statistically significant association between HCV infection and WM has not been found.<sup>5</sup>

In relation to familial predisposition, an association is estimated in 20% of cases.<sup>6,7</sup> In first degree family relations there is a high risk of developing lymphoproliferative diseases, which is twenty times higher for WM/LPL.<sup>8</sup>

## **PATHOPHYSIOLOGY**

It is believed that WM originates in memory B-lymphocytes.<sup>9,10</sup> These lymphocytes descend from B-lymphocytes that proliferate in the germinal centers of lymph nodes (post-germinal center B-lymphocytes), accumulating all the genetic changes that occur in these centers. Thus, in most cases, the neoplastic B cells present somatic hypermutation in the genes coding the hypervariable regions of the immunoglobulin heavy chains ( $V_H$  genes).<sup>11,12</sup> However, in some cases, the neoplastic B-cells are derived from B-lymphocytes which have undergone somatic mutation outside of germinal centers.<sup>13</sup> In other cases, there is no evidence of somatic mutations in the  $V_H$  genes, which may indicate that they are derived from pre-germinal center B-lymphocytes, such as “virgin” B-lymphocytes.<sup>12</sup>

In relation to the mechanisms involved in the pathophysiology of WM, the blocking of immunoglobulin isotype switching and the role of cytokines is noteworthy.

Most malignant cells in WM express surface IgM and IgD, suggesting an intrinsic incapacity to switch isotypes.<sup>13</sup> This “block” may be related to the absence/dysfunction of the activation-induced cytidine deaminase (AID) enzyme, which is involved in somatic hypermutation and the immunoglobulin isotype switching process.<sup>11,13</sup>

Although isotype switching is rarely seen in WM, according to some studies it is possible that it occurs *ex vivo* and *in vivo*. Kriangkum et al.<sup>11</sup> demonstrated that AID may be induced *ex vivo*, by stimulation with CD40L and interleukin-4 (IL-4). Another study showed the possibility of isotype switching occurring *in vivo*.<sup>14</sup>

Mast cells and various cytokines play an important role in the development of the disease.<sup>15</sup> Cytokines may be important for angiogenesis, increased bone resorption, proliferation, survival of malignant cells, and secretion of monoclonal IgM.

In WM, malignant B-lymphocytes express the receptor CD27,<sup>13</sup> which can be found in the membrane of memory B-lymphocytes and in soluble form (sCD27) in high concentrations in the serum.<sup>15</sup> sCD27 activates bone marrow mast cells by binding to CD70. Activated mast cells secrete growth and survival factors for B-lymphocytes

such as CD40L and APRIL (proliferation-inducing ligand),<sup>15</sup> which may contribute to lymphoplasmocytoid differentiation of malignant cells in the bone marrow.

## **CLINICAL SYMPTOMS**

The clinical presentation of WM varies. Most of the patients present clinical signs/symptoms related to IgM hypergammaglobulinemia and/or LPL infiltration in organs and tissues, especially bone marrow. However, some patients do not exhibit any clinical symptoms when diagnosis is made.<sup>16</sup>

Blood hyperviscosity determines hemorheological changes and is one of the most important characteristics of WM; however, it is observed in less than 15% of patients upon diagnosis. The large size of the monoclonal IgM molecule and its high concentration contribute to increased blood viscosity and vascular resistance, compromising the blood flow to oxygenate tissues.<sup>17</sup>

The main clinical manifestations associated with the hyperviscosity syndrome are bleeding (epistaxis, bleeding gums and gastrointestinal bleeding), ocular changes (papilledema, blindness, blurred vision and retinal changes: hemorrhage, exudates, dilatation and segmentation of the retinal veins, venous thrombosis), neurological changes (headache, dizziness, syncope, deafness, ataxia, diplopia, drowsiness and even seizures) and cardiac changes (heart failure).<sup>18</sup>

The symptoms of hyperviscosity generally manifest when the concentration of monoclonal IgM is greater than 5000 mg/dL or when the serum viscosity reaches 4-5 cP (reference range: 1.4 to 1.8 cP). However, the serum viscosity is not always proportional to the concentration of IgM and its relationship to symptoms is not linear.<sup>16</sup>

Type I cryoglobulinemia (monoclonal IgM cryoglobulinemia) is associated with lymphoproliferative diseases such as WM, and is detected in approximately 20% of patients, while symptomatic in only 5% of cases.<sup>19</sup> The precipitation of monoclonal IgM cryoglobulin is also responsible for some clinical symptoms, such as Raynaud's phenomenon, acrocyanosis, purpura and necrosis of body regions most exposed to the cold. It is also responsible for the development of distal symmetrical sensorimotor polyneuropathy or multiple mononeuropathy with axonal degeneration.<sup>20,21</sup>

Monoclonal IgM can cause platelet dysfunction by binding to IIIa and Ib glycoproteins on the surface of platelets or due to nonspecific interactions with platelets.<sup>9</sup> It may also neutralize the activity of several coagulation factors (fibrinogen, prothrombin, factors V, VII, VIII, IX, X, and Von Willebrand factor),<sup>9,22</sup> triggering hemostatic

disorders that are the source of hemorrhagic manifestations.

Monoclonal IgM may exhibit “cold agglutinin” activity, binding to erythrocyte antigens at a temperature lower than physiological temperature, determining the development of chronic cold antibody hemolytic anemia. This monoclonal immunoglobulin is generally IgM Kappa, which often interacts with I/i antigens on the surface of erythrocytes.<sup>23,24</sup> Anemia manifests in less than 10% of patients and is generally associated with “cold agglutinins” levels above 1:1000.<sup>25</sup> The reduction in the temperature of blood flowing through the peripheral blood vessels favors the binding of IgM “cold agglutinins” to the surface of erythrocytes.<sup>26</sup> This agglutination of erythrocytes in peripheral blood vessels is responsible for Raynaud’s phenomenon, acrocyanosis and *livedo reticularis*, which is reversible when large blood circulation resumes.

Type II cryoglobulinemia (mono and polyclonal) is characterized by the deposition of monoclonal IgM-polyclonal IgG immunocomplexes at the level of blood vessels, with consequent activation of the complement.<sup>17</sup> The main clinical manifestations are vasculitis, *purpura*, arthralgia, digital necrosis, Raynaud’s phenomenon, peripheral neuropathy in lower limbs, renal impairment (*proteinuria*, *hematuria*, nephrotic syndrome), and liver impairment (hepatomegaly, liver dysfunction).

Around 20% of patients may be experiencing neurological symptoms at the time of diagnosis. The most frequent neurological disorder is a demyelinating distal symmetrical sensorimotor peripheral neuropathy, which manifests itself slowly and progressively, causing paresthesia and asthenia. About 50% of these patients have myelin-associated glycoprotein antibodies (MAG anti-antibodies).<sup>27</sup> These are generally monoclonal IgM kappa and are often involved in demyelinating neuropathies.

Monoclonal IgM can also connect nonspecifically to multiple antigens of the peripheral nerves, triggering axonal impairment.<sup>20,28</sup>

The biological function of various tissues and/or organs may be altered by the formation and deposition of monoclonal IgM aggregates, however, the clinical manifestations related to their deposition are not frequent.

The deposition of monoclonal IgM in the basal membrane of the epidermis is associated with bullous skin disease.<sup>29</sup> If it occurs at the level of the dermis it contributes to the formation of papular-nodular lesions on the surface (*Macroglobulinemia cutis*).<sup>30,31</sup> Some patients may have chronic *urticarial erythema*, fever and arthralgia (Schitzler syndrome).<sup>32</sup>

The deposition of monoclonal IgM in the *lamina propria* and/or submucosa of the intestine can be associated with diarrhea, malabsorption and gastrointestinal bleeding.<sup>33</sup>

Renal failure is not very common; however, monoclonal IgM may accumulate in the renal *glomeruli*, forming subendothelial deposits that clog glomerular capillaries.<sup>34</sup> In this case, there may be moderate but reversible *proteinuria*, being the majority of patients asymptomatic.

In primary or light chain amyloidosis (AL amyloidosis), amyloid fibrils may be deposited in the heart, kidneys, liver, lungs and peripheral nerves.<sup>20</sup> Cardiac and pulmonary involvement is more frequent in patients with amyloidosis associated with monoclonal IgM.<sup>35,36</sup> AL amyloidosis may be related to the development of symmetrical or asymmetrical sensory-motor polyneuropathy. Patients experience pain, the sensation of “electric shocks” and thermal sensitivity in the lower limbs. AL amyloidosis may further affect the autonomic nervous system, causing diarrhea, hypotension, impotence and bladder dysfunction.<sup>28</sup>

The deposition of amyloid A protein (AA amyloidosis) has been documented, although rare,<sup>37,38</sup> and may occur in the kidneys and intestines, causing nephrotic syndrome and intestinal malabsorption.<sup>39</sup>

IgG and IgA hypogammaglobulinemia may occur simultaneously with monoclonal IgM hypergammaglobulinemia, which can contribute to recurrent respiratory tract infections, but its cause is not well understood and could be associated with alterations in the development of plasma cells and/or the production of immunoglobulins.<sup>40</sup>

LPL primarily involves the bone marrow, but the disease can reach the lymph nodes, spleen and liver, among other organs. Lymphoplasmocytoid/plasmacytic infiltration is responsible for asthenia, fatigue, recurrent fever, night sweats, weight loss, cytopenia, lymphadenopathy and organomegaly.<sup>17</sup>

Fatigue is one of the most common symptoms and is often associated with normocytic normochromic anemia; around 80% of symptomatic patients have moderate to severe anemia.<sup>27</sup> Anemia is not only due to the change in medullary erythropoiesis. Other factors may contribute to its aggravation, such as gastrointestinal bleeding, hyperhemolysis, and hyperviscosity itself, which may cause a decrease in the erythropoietin synthesis.<sup>41</sup> It should be noted that false anemia may be observed in some patients caused by the high concentration of monoclonal IgM, which contributes to the increase in plasma volume and consequent hemodilution.

Extramedullary infiltration is uncommon, and may affect the articular and periarticular structures, gastrointestinal tract, lungs, kidneys, skin, eyes and central nervous system.<sup>17,27,42</sup>

The symptoms of malabsorption, diarrhea, obstipation or bleeding may indicate involvement of the gastrointestinal tract.<sup>43-46</sup> Some patients have cellular infiltration at the pulmonary parenchymal level,<sup>47,48</sup> being coughing the most common symptom, followed by dyspnea and chest pain. Renal infiltration has also been reported,<sup>49</sup> as well as cutaneous infiltration (maculopapular lesions, plaques or nodules)<sup>7,50</sup> and infiltration of periorbital structures, such as the tear gland and retro-orbital lymphoid tissue (ocular tremors).<sup>51,52</sup>

The infiltration of malignant cells in the central nervous system is responsible for a rare neurological disorder called Bing-Neel syndrome. Associated symptoms are nystagmus, diplopia, vertigo, memory loss, mental confusion, motor dysfunction and eventually coma.<sup>17,53</sup>

## DIAGNOSIS

Table 1 presents the diagnostic criteria for WM. The detection of IgM monoclonal gammopathy is important for diagnosis, but the serum concentration presents a great variability between individuals.<sup>16</sup>

For diagnosis, a bone marrow biopsy is crucial to assess the extent of neoplastic infiltration, the infiltration pattern and cellular morphology. In WM, medullary infiltrate consists of a monoclonal cellular population of small B-lymphocytes, in different maturation stages: small lymphocytes, lymphoplasmacytoid lymphocytes and plasma cells.

The level of differentiation of the infiltrate is variable, ranging from lymphoplasmacytoid (47% of cases), consisting of small cells and plasmacytoid lymphocytes,

to lymphoplasmacytic (42%), with predominantly small lymphocytes and plasma cells. The polymorphic state (11%) is characterized by a broad spectrum of these many cells.

A high number of mast cells in the medullary infiltrate is frequent, and this finding may help in the differential diagnosis.

LPL may eventually evolve into a more aggressive form of lymphoma such as as diffuse large B-cell lymphoma.<sup>54</sup> This evolution is accompanied by worsening of clinical symptoms, with development of profound cytopenia, organomegaly and extramedullary cellular infiltration.<sup>54</sup>

In the peripheral blood, plasmacytoid lymphocytes are sometimes observed, but leukemic symptoms are rarely observed.

Immunophenotyping should be interpreted simultaneously, verifying its consistency with the results of a bone marrow biopsy. In practice, IgM monoclonal gammopathy associated with the expression of IgM on neoplastic B-lymphocytes with a CD19<sup>+</sup>, CD20<sup>+</sup>, CD5<sup>-</sup>, CD10<sup>-</sup> and CD23<sup>-</sup> phenotype and intertrabecular pattern of bone marrow infiltration is sufficient for the diagnosis of MW<sup>16</sup> (Table 1). Nevertheless, the phenotypic characteristics are not always typical and in about 10-20% of cases positivity for CD5, CD10 or CD23 has been described.<sup>17,55,56</sup> Other common phenotypic features which are not specific but may be useful for the differential diagnosis with other lymphoproliferative diseases are the expression of sIgD, CD22, CD79a, PAX5, Bcl2, FMC7, CD25 and CD27 and the absence of expression of BCL6, CD103, CD138, CD56 and CD75. Some of these markers are particularly useful for studying the bone marrow infiltrate in the bone biopsy through immunohistochemical and other studies for the immunophenotypic characterization of B-lymphocytes by flow cytometry.

**TABLE 1** Clinical and laboratory characteristics of Waldenström's macroglobulinemia

IgM monoclonal gammopathy of varying concentration
Bone marrow biopsy: ≥10% infiltration by small B-lymphocytes with plasmacytoid/plasmacytic differentiation
Bone marrow biopsy: generally intertrabecular infiltration pattern
Immunophenotyping of B-lymphocytes: CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD5 <sup>-</sup> , CD10 <sup>-</sup> , CD23 <sup>-</sup> ; sIgM <sup>+</sup> (monoclonal)
Other immunophenotypic characteristics of neoplastic B-lymphocytes: sIgD <sup>+</sup> , CD22 <sup>+</sup> , CD79a <sup>+</sup> , PAX5 <sup>+</sup> , Bcl2 <sup>+</sup> , FMC7 <sup>+</sup> , CD25 <sup>+</sup> , CD27 <sup>+</sup> , BCL6 <sup>-</sup> , CD103 <sup>-</sup> , CD138 <sup>-</sup> , CD56 <sup>-</sup> , CD75 <sup>-</sup>
Cytogenetic studies: over 50% of cases present deletions (del) 6q

sIgM – Surface immunoglobulin M.

Note: Immunophenotypic variations may occur. Other lymphoproliferative diseases, including marginal zone B-cell lymphoma, chronic lymphocytic leukemia and mantle cell lymphoma should be excluded.

The assessment of the clinical status of patients involves several examinations and laboratory tests (Table 2).

When interpreting the results it is important to consider that some parameters could be altered because the monoclonal IgM may interfere in several measurements performed in automated analyzers, especially in the evaluation of HDL cholesterol, bilirubin, inorganic phosphate, LDL cholesterol, C-reactive protein, creatinine, glucose, urea, iron and calcium ions.<sup>27</sup>

## DIFFERENTIAL DIAGNOSIS

It is fundamental to distinguish WM from other disorders that could be clinically confused with this disease.

Differential diagnosis (Table 3) is important for the exclusion of neoplasms potentially secreting monoclonal IgM and which can also present lymphocytes with lymphoplasmacytoid differentiation in the bone marrow. This group includes marginal zone lymphomas,<sup>57</sup> chronic lymphocytic leukemia (CD5<sup>+</sup>, CD23<sup>+</sup>), mantle cell lymphoma (CD5<sup>+</sup>, CD23<sup>-</sup>), follicular lymphoma (CD10<sup>+</sup>) and multiple myeloma (CD138<sup>+</sup>, CD38<sup>+</sup>, CD56<sup>+</sup>).<sup>17,57</sup>

The differentiation between symptomatic WM, asymptomatic WM and IgM monoclonal gammopathy of undetermined significance (MGUS) is important since the latter patients present risk of progression to symptomatic WM of 1.5%/year.<sup>58,59</sup> This differs from asymptomatic

**TABLE 2** Laboratory assessment in patients with clinical suspicion of Waldenström's macroglobulinemia

Laboratory exam	Clinical justification
Electrophoresis of serum proteins	Detection of monoclonal gammopathy - homogeneous peak, high, narrow base, usually in the area of gamma globulins
Electrophoresis of urinary proteins (24-hour urine)	
Immunofixation of serum and urinary proteins	Characterize the immunoglobulin: heavy chain and light chain
Bone marrow biopsy	Assess the bone marrow infiltration by lymphocytes, the infiltration pattern and cell morphology
Erythrocyte sedimentation rate	Frequently raised
Cytogenetic studies	Differential diagnosis of other malignancies of B-lymphocytes secreting monoclonal IgM
Blood test	Evaluation of thrombocytopenia and anemia, which is usually normocytic and normochromic
- Reticulocyte count	
- Concentration of haptoglobin, indirect bilirubin and lactate dehydrogenase	Search autoimmune hemolytic anemia. Useful in patients with Raynaud's syndrome, acrocyanosis or limb ulceration
- Research, identification and quantification of "cold agglutinins"	
- Direct Coombs Test and title of "cold agglutinins"	
Serum viscosity	Determine if the patient has signs and symptoms of hyperviscosity or IgM concentration >4000 mg/dL
Eye examination - ophthalmoscopy	Justified in the event of changes in vision
Urea, creatinine and transaminases (AST and ALT)	Evaluation of renal and hepatic function
β2-microglobulin	Relevant for prognosis
IgG and IgA	Predisposition to respiratory infections
TTPa, TP, TT	In patients with bleeding diathesis and a tendency to bruise
Detection and semi-quantification of anti-MAG, anti-SGPG, anti-GM1, anti-sulfatide antibodies	In patients with peripheral neuropathy, such as progressive symmetrical numbness of the limbs, burning sensation and tingling, pain in the feet and hands
Screening of AL amyloidosis - electrophoresis and immunofixation of urinary proteins (24-hour urine)	In suspected cases of AL amyloidosis
Confirmation of AL amyloidosis test - abdominal fat aspirate	
Electromyography	In patients who have impaired motor function
Computed tomography of the abdomen, trunk and pelvis	Detection of organomegaly (e.g. spleen, liver) and lymphadenopathy

AST, aspartate aminotransferase; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; PT, prothrombin time; TT, thrombin time; MAG, myelin-associated glycoprotein; SGPG, sulfate-3-glucuronoyl paragloboside; GM1, GM1 ganglioside.

**TABLE 3** Differential diagnosis of Waldenström's macroglobulinemia (WM) (Adapted from Fonseca and Hayman 2007<sup>76</sup>)

Neoplasm	Immunophenotype	Pattern of marrow infiltration and cell morphology	Cytogenetic abnormalities
Waldenström's Macroglobulinemia	sIgM <sup>+</sup> (kappa to lambda ratio 5:1), sIgD <sup>+</sup> , CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD22 <sup>+</sup> , CD79a <sup>+</sup> , PAX5 <sup>+</sup> , Bcl2 <sup>+</sup> , FMC7 <sup>+</sup> , CD5 <sup>+/−</sup> , Bcl6 <sup>−</sup> , CD10 <sup>−</sup> , CD23 <sup>−</sup> , CD25 <sup>+</sup> , CD27 <sup>+</sup> , CD103 <sup>−</sup> , CD138 <sup>−</sup> , CD56 <sup>−</sup>	Generally intertrabecular; Small lymphocytes with plasmacytoid differentiation	Most patients have a normal karyotype; The most frequent cytogenetic alterations are 6q21-23 deletions
Multiple Myeloma	clg <sup>+</sup> , slg <sup>−</sup> , CD19 <sup>−</sup> , CD20 <sup>−</sup> , PAX5 <sup>−</sup> , CD38 <sup>+</sup> , CD79a <sup>−</sup> , CD138 <sup>+</sup> , CD56 <sup>+</sup>	Nodular, diffuse, interstitial; Plasma cells with different degrees of maturation	t(11;14) (q13;q32)
B-cell chronic lymphocytic leukemia	sIg <sup>+</sup> (weak), CD43 <sup>+</sup> (weak), CD20 <sup>+</sup> (weak), CD19 <sup>+</sup> , CD23 <sup>+</sup> , CD5 <sup>+</sup> , CD23 <sup>+</sup> , CD10 <sup>−</sup> , CD79b/CD22 <sup>−</sup> , FMC7 <sup>−</sup> , Cyclin D1 <sup>−</sup>	Nodular, interstitial, diffuse or mix of all three; Small lymphocytes with dense nucleus, aggregated chromatin, no visible <i>nucleoli</i> and reduced cytoplasm	Del 13q14 (50% of cases); Del 11q (20% of cases); Trisomy of chromosome 12 (20% of cases); Del 17p; Presence of ZAP-70 <sup>+</sup> (Tyrosine Kinase of 70 Kda associated to the zeta chain of the T lymphocyte receptor complex)
Mantle cell lymphoma	sIgM <sup>+</sup> , sIgD <sup>+/−</sup> , lambda light chain restriction, CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD5 <sup>+</sup> , CD43 <sup>+</sup> , FMC-7 <sup>+</sup> , Cyclin D1 <sup>+</sup> , CD10 <sup>−</sup> , BCL-6 <sup>−</sup> , CD23 <sup>−</sup>	Variable infiltration pattern. Lymphocytes are small or medium in size with irregular nucleus	t(11;14) (q13;q32)
Follicular lymphoma	sIg <sup>+</sup> , CD10 <sup>+</sup> , CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD21 <sup>+</sup> , CD22 <sup>+</sup> , CD79a <sup>+</sup> , Bcl-2 <sup>+</sup> , Bcl-6 <sup>+</sup> , CD43 <sup>+</sup> , CD5 <sup>+</sup> , CD23 <sup>−</sup> , CD43 <sup>−</sup>	Paratrabecular infiltration; Centrocytes (small cells with "cleaved" <i>nuclei</i> and reduced cytoplasm) and centroblasts (large cells with round or oval nuclei, vesicular chromatin, and low basophilic cytoplasm)	t(14;18)(q32;q21) (70-95% of cases).
Extranodal marginal zone lymphoma, MALT	sIgM <sup>+</sup> (generally), light chain restriction (generally), CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD21 <sup>+</sup> , CD35 <sup>+</sup> , CD22 <sup>+</sup> , CD79 <sup>+</sup> , CD43 <sup>+/−</sup> , CD5 <sup>+</sup> , CD10 <sup>−</sup> , CD23 <sup>−</sup> , CD11c <sup>+</sup> (weak)/CD11c <sup>−</sup>	Variable	Trisomy 3 (60% of cases); t(11;18) (q21;q21) (25%-50% of cases); t(1;14) (p22;q32); t(11;18) (q21;q22); t(14;18) (q32;q21); t(3;14) (p13;q32)
Nodal marginal zone lymphoma	Most lymphomas have a similar immunophenotype to MALT lymphoma, others have a similar immunophenotype to splenic marginal zone lymphomas	Variable	Trisomy 3; t(11;18) (q21;q21)
Splenic marginal zone lymphoma	sIgM <sup>+</sup> , IgD <sup>+</sup> (generally), CD19 <sup>+</sup> , CD20 <sup>+</sup> , CD22 <sup>+</sup> , Bcl-2 <sup>+</sup> , CD79a <sup>+</sup> , CD5 <sup>+</sup> , CD23 <sup>−</sup> , CD10 <sup>−</sup> , CD43 <sup>−</sup> , CD25 <sup>−</sup> , CD103 <sup>−</sup> , Cyclin D1 <sup>−</sup>	Nodular, interstitial	Chromosomal gains: 3q (30-40% of cases), 5q (28%), 12q (24%), 20q (24%), 9q (21%), 4q (17%); Trisomy 3 (17%); Del 7q; Del 6q and Del 17p – Genetic alterations associated with clinical progression of the disease

clg – cytoplasmic immunoglobulin, slg, surface immunoglobulin; MALT, mucosa-associated lymphoid tissue.

WM due to the lower concentration of monoclonal IgM (< 3 g/dL) and absence of bone marrow infiltration (<10%). The risk of progression from asymptomatic to symptomatic WM is 6%/year, and only 55% of these patients will show progression within 5 years<sup>3</sup>.

## PROGNOSIS OF SYMPTOMATIC WM

The International Prognostic Staging System for Waldenström Macroglobulinemia adopts five variables that correlate with poor survival of patients under treatment: age > 65 years,  $\beta$ 2-microglobulin concentration >3 mg/L, platelets count  $\leq 100 \times 10^9/L$ , monoclonal IgM concentration > 7000 mg/dL, and hemoglobin concentration  $\leq 11.5$  g/dL.<sup>60</sup> The absence or presence of one or more prognostic factors categorizes the patient into 3 risk levels: low (0 -1 risk factor, excluding age), intermediate (2 risk factors and age > 65 years) or high (more than 3 risk factors).<sup>60</sup>

Based on the degree of risk, it is possible to estimate the average/overall survival. In patients at low risk, the average survival time is 12 years, and treatment should involve low toxicity, preserving quality of life. The use of this system in symptomatic patients that are candidates for treatment enables tailoring treatment to the patient, taking into account the estimated average survival.

In a recent study, high concentrations of *lactate dehydrogenase* (> 250 IU/L) were also seen as a poor prognosis factor, especially in high risk patients.<sup>61</sup>

## TREATMENT

Clinical decision to prescribe therapy takes into account different factors such as patient age, clinical manifestations, prognostic factors, quality of life and patient survival potential, the risk/benefit and cost/benefit of treatment, effectiveness and side effects.

The treatment of asymptomatic patients does not improve their quality of life and survival;<sup>3</sup> biannual clinical observation is the recommended option in these cases if hematologic function is preserved.<sup>3</sup> There is a study that suggests bimonthly/quarterly follow-ups during the first year after diagnosis and, if remaining stable, monitoring should be quarterly/half-yearly in the following years.<sup>62</sup>

Patients with WM are candidates for treatment if they have clinical evidence of aggressive disease progression or if they have had clinical and laboratory manifestations associated with WM, such as lymphadenopathy or splenomegaly, symptoms of hyperviscosity, severe peripheral neuropathy, AL amyloidosis (resulting in tissue deposition of light immunoglobulin chains), cryoglobulinemia, autoimmune hemolytic anemia, hemoglobin concentration <10 g/dL and/or platelet count <100x10<sup>9</sup>/L.<sup>63</sup>

In fact, the choice of treatment is a critical option and should not be taken so as to limit future options, since all patients will inevitably present relapses after initial treatment, requiring treatment.<sup>3</sup> Age, the presence of cytopenia, the need to control the disease and the possibility of autologous stem cell transplantation should be considered in the approach to treatment.<sup>63</sup>

First-line therapy includes alkylating agents, purine analogs and monoclonal anti-CD20 antibodies.<sup>63</sup> Treatment with alkylating agents may cause cytopenias and myelosuppression, and should be avoided in patients that are candidates for autologous transplantation.<sup>63,64</sup> Purine analogs may be responsible for the development of myelodysplasia and acute myeloid leukemia.<sup>63,65</sup>

The Mayo Clinic has developed a therapeutic approach adapted to the clinical characteristics of the patient.<sup>3</sup> Most symptomatic patients are treated with Rituximab as monotherapy or combined with chemotherapy. Monotherapy is recommended in symptomatic patients with moderate hematological impairment, in patients with neuropathy associated with the IgM autoantibody, and in cases of hemolytic anemia resistant to corticosteroids.<sup>3</sup>

Rituximab is an IgG1 anti-CD20 monoclonal antibody. The connection to the CD20 receptor on B-lymphocytes activates the complement cascade, leading to the formation of the membrane attack complex that induces cell lysis.<sup>66</sup> This antibody also activates natural killer cells by binding to receptors for the Fc fragment of IgG (Fc $\gamma$ R), leading to cell lysis. The fragments of complement component C3, together with rituximab, are recognized by the membrane of macrophages, binding to receptors for complement component C3 and Fc $\gamma$ R receptors, respectively, and activating phagocytosis.<sup>66,67</sup> The genetic polymorphism of Fc $\gamma$ R receptors may condition the treatment response,<sup>68</sup> and a correlation has been observed between polymorphisms at position 158 of the Fc $\gamma$ RIIIa (CD16) receptor and the response to rituximab.

At the start of rituximab treatment, some patients have a paradoxical and often transient increase in serum concentrations of IgM (IgM flare), which can persist for up to 4 months and is not indicative of treatment failure.<sup>69,70</sup> The underlying mechanism remains unclear, but two hypotheses have been proposed - release of intracellular IgM resulting from rituximab-mediated cell death and cell signaling mediated by binding to CD20.<sup>71</sup>

In patients requiring urgent control of the disease, plasmapheresis is indicated if they have clinical manifestations of moderate to severe hyperviscosity, cryoglobulinemia and cytopenias caused by the action of the monoclonal IgM autoantibody.<sup>62,3</sup> Usually 2 to 3 plasmapheresis sessions

are necessary to reduce the concentration of IgM from 30 to 60%. The sessions should be repeated daily until symptoms subside or until normalization of serum viscosity. Subsequent treatment should be started quickly, as the concentration of IgM will return to its initial level after 4 to 5 weeks.<sup>62</sup> These patients should be treated with the dexamethasone, rituximab and cyclophosphamide (DRC) combination regimen. The main reasons for choosing this regimen in these patients are the good treatment tolerance, reduced myelosuppression and the lack of toxicity for stem cells.<sup>3,65</sup>

In patients with relapses or who are refractory to therapy, the choice of treatment depends on the first-line treatment already utilized, the quality/duration of the response and other variables, such as age, tolerance to initial treatment, and also the possibility of the patient being a candidate for stem cell transplantation.<sup>63</sup>

The reuse of the first-line treatment is recommended if the response to initial treatment was maintained without maintenance for at least 12 months. Otherwise, another first-line agent or combination therapy should be used.<sup>63</sup>

In patients with short-term remission or resistance to initial treatment, therapy with a drug of different pharmacological class as monotherapy or combined is recommended. In association therapy, a regime using rituximab, fludarabine and cyclophosphamide is highlighted; however, the latter should be avoided in younger patients and candidates for autologous stem cell transplantation.<sup>63</sup>

The use of bortezomib (proteasome inhibitor) has proven promising, as well as alemtuzumab (anti-CD52 monoclonal antibody) datalidomida, enzastaurin (protein kinase C inhibitor), everolimus (inhibitor of mammalian target of rapamycin - mTOR) and perifosine (Akt inhibitor).<sup>62,64,72</sup> Histone deacetylase inhibitors treatment agents, such as panobinostat (LBH589), new proteasome inhibitors, such as carfilzomib, human anti-CD20 monoclonal antibody, such as ofatumumab, and alkylating agents, such as bendamustine, also seem to be promising agents.<sup>72</sup>

Transplantation of hematopoietic stem cells is indicated in younger patients with multiple recurrences or who have been refractory to previous treatments.<sup>62</sup> Autologous transplantation is associated with improved survival and long periods without disease progression, and should be considered in all candidate patients presenting relapse.<sup>3</sup>

The concentration of monoclonal IgM is one of the parameters most commonly used among the criteria for assessing response to treatment. However, this biomarker is not always reliable, since its concentration can be affected by the treatment itself.<sup>62</sup>

Taking into account the criteria for treatment response, complete response is observed when IgM serum levels normalize with complete disappearance of IgM monoclonal protein (by immunofixation), histological evaluation of the bone marrow shows no evidence of disease, and all symptoms, lymphadenopathy and/or organomegaly are resolved. Partial response is considered in a scenario of  $\geq 50\%$  decrease in the monoclonal IgM serum concentration, decreased lymphadenopathy/organomegaly and absence of new symptoms and/or signs of active disease on electrophoresis of serum proteins compared to the baseline values. A minimal response is observed when the reduction in electrophoresis of monoclonal IgM is  $<50$  but  $\geq 25\%$ , and no new symptoms and/or signs of active disease are observed. The stable disease corresponds to cases in which the value of monoclonal IgM relative to baseline undergoes a reduction of  $<25\%$  and increases  $<25\%$ , with no progression of lymphadenopathy/organomegaly and cytopenias, and no significant clinical signs or symptoms. The disease is considered progressive when there is an increase in the detectable amount of protein electrophoresis and monoclonal IgM serum levels  $\geq 25\%$  (confirmed by a second assessment) or progression of complications resulting from the disease or symptoms attributed to WM.<sup>73</sup>

The concentration of sCD27 and assessment of the amount of monoclonal free light chains have been presented as potential biomarkers for laboratory monitoring of therapy.<sup>74,75</sup> The investigation of alternative biomarkers is essential for a more reliable and less invasive clinical evaluation.

## RESUMO

Macroglobulinemia de Waldenström - uma revisão.

A macroglobulinemia de Waldenström (MW) é uma doença linfoproliferativa dos linfócitos B, caracterizada por um linfoma linfoplasmocítico na medula óssea e por hipergamaglobulinemia monoclonal de tipo IgM. Foi descrita pela primeira vez em 1944, por Jan Gösta Waldenström, que descreveu dois doentes com hemorragia oronasal, adenopatias, anemia, trombocitopenia, velocidade de sedimentação eritrocitária e viscosidade sérica elevadas, radiografia óssea normal e medula óssea infiltrada por células linfóides.

A MW é uma doença rara com um percurso clínico normalmente indolente, atingindo principalmente os indivíduos com idades entre 63 e 68 anos. A maioria dos doentes apresenta sintomas e manifestações clínicas relacionadas com a

hiperviscosidade, resultante da gamopatia monoclonal IgM e/ou com as citopenias, resultantes da infiltração medular pelo linfoma. O diagnóstico diferencial com outros linfomas é essencial para a avaliação do prognóstico e a abordagem terapêutica.

O tratamento dos doentes com MW assintomática não melhora a qualidade de vida do doente nem aumenta a sua sobrevivência, recomendando-se o acompanhamento clínico. Para o tratamento dos doentes sintomáticos, são usados agentes alquilantes, análogos das purinas e anticorpos monoclonais anti-CD20. No entanto, a doença é incurável e a resposta à terapêutica nem sempre é favorável. Estudos relativamente recentes mostram resultados promissores com o bortezomibe, um inibidor dos proteossomas, e alguns doentes respondem à talidomida. Nos doentes com recidivas ou refratários à terapêutica, pode-se indicar o transplante autólogo.

O objetivo deste trabalho é descrever, de forma detalhada, o conhecimento atual sobre a fisiopatologia da MW, as principais manifestações clínicas, o diagnóstico, o prognóstico e o tratamento.

**Palavras-chave:** macroglobulinemia de Waldenström; hipergamaglobulinemia; IgM; linfócitos B; prognóstico.

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